# Bezlotoxumab (MK-6072)
# FDA Antimicrobial Drugs Advisory Committee Meeting

## June 9, 2016

*Merck Research Laboratories (Merck)*

# Agenda

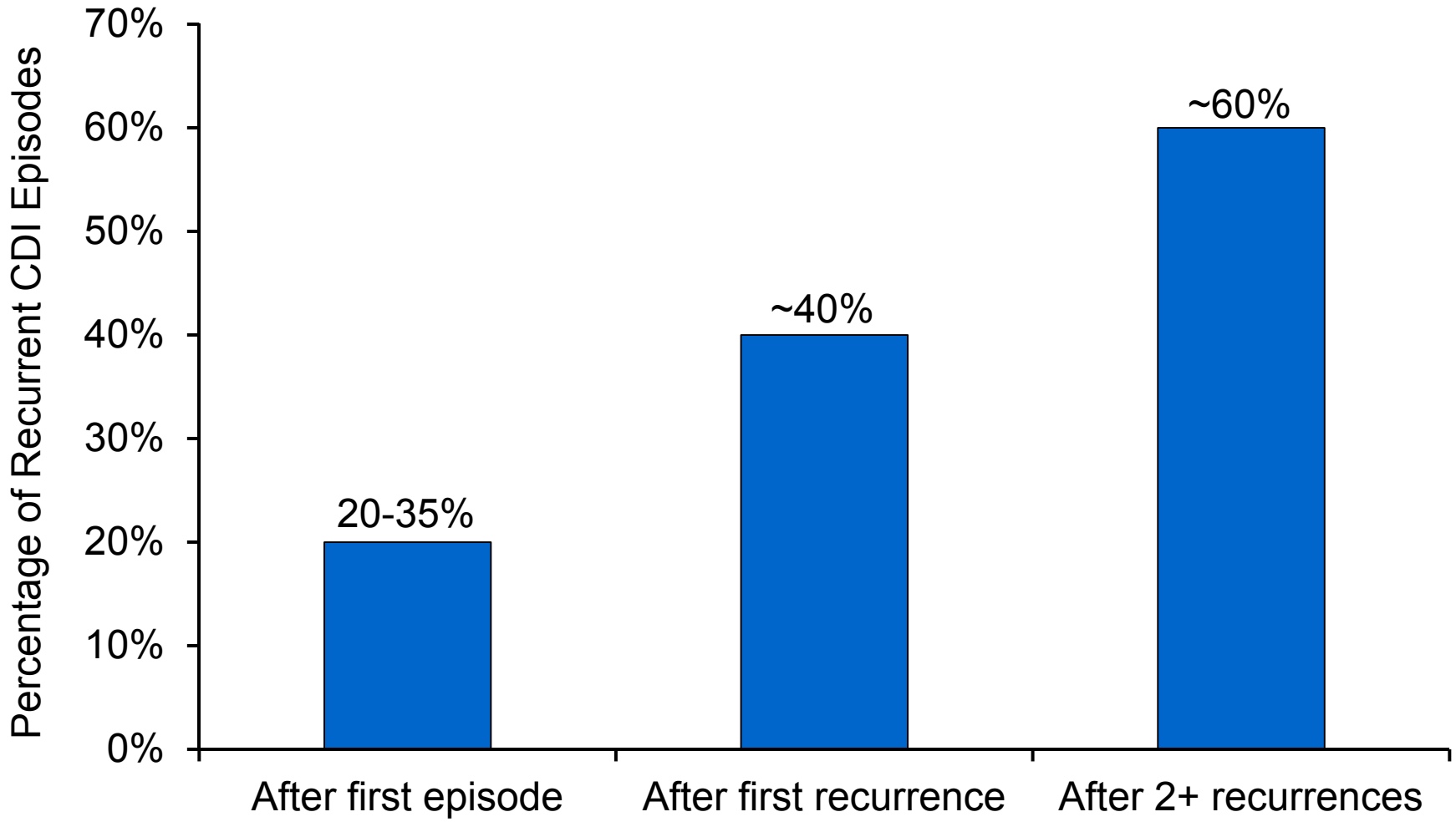
| | |
|---|---|
| **Bezlotoxumab Introduction** | **Donnette Staas, PhD**<br>Director, Regulatory Affairs<br>Merck |
| **Clinical Program: Overview and Efficacy** | **Dalya Guris, MD, MPH**<br>Executive Director, Clinical Research<br>Merck |
| **Clinical Program: Safety** | **Yoshihiko Murata, MD, PhD**<br>Director, Clinical Research<br>Merck |
| **Benefit/Risk and Conclusions** | **Mark H. Wilcox, MD, FRCPath**<br>Professor of Medical Microbiology<br>Leeds Teaching Hospitals &<br>University of Leeds<br>Lead on *C. difficile,* Public Health England |

# *C. difficile* Infection: An Urgent Public Health Threat

- *C. difficile*: Spore-forming organism ubiquitous in hospital environment
  - *C. difficile* infection (CDI) has become the leading cause of hospital-acquired infection
  - Incidence of community-acquired CDI is also increasing
- Estimated 453,000 incident CDI episodes in the US in 2011[1]
  - 83,000 first recurrences of CDI
  - 29,000 CDI-associated deaths (greater than MRSA and MDR Gram-negative infections combined)
- CDC declared *C. difficile* 1 of 3 **urgent** antibiotic resistance threats

[1] Lessa, et al. NEJM. 2015.
MDR=multidrug-resistant; MRSA=methicillin-resistant *Staphylococcus aureus*.

# *C. difficile* Infection Recurrence[1]

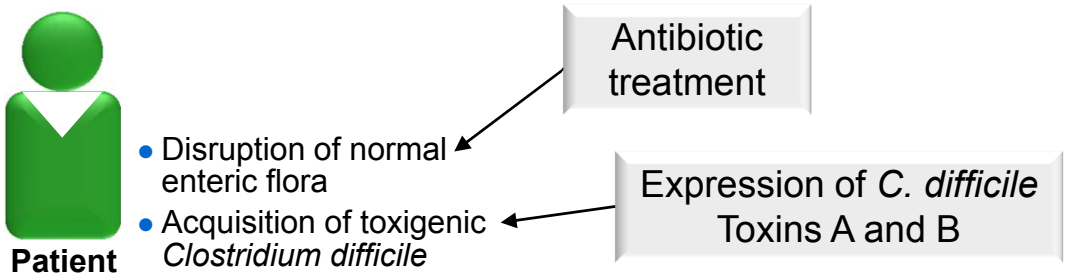



[1] McFarland, et al. Am J Gastro. 2002.

# CDI: Current Therapy

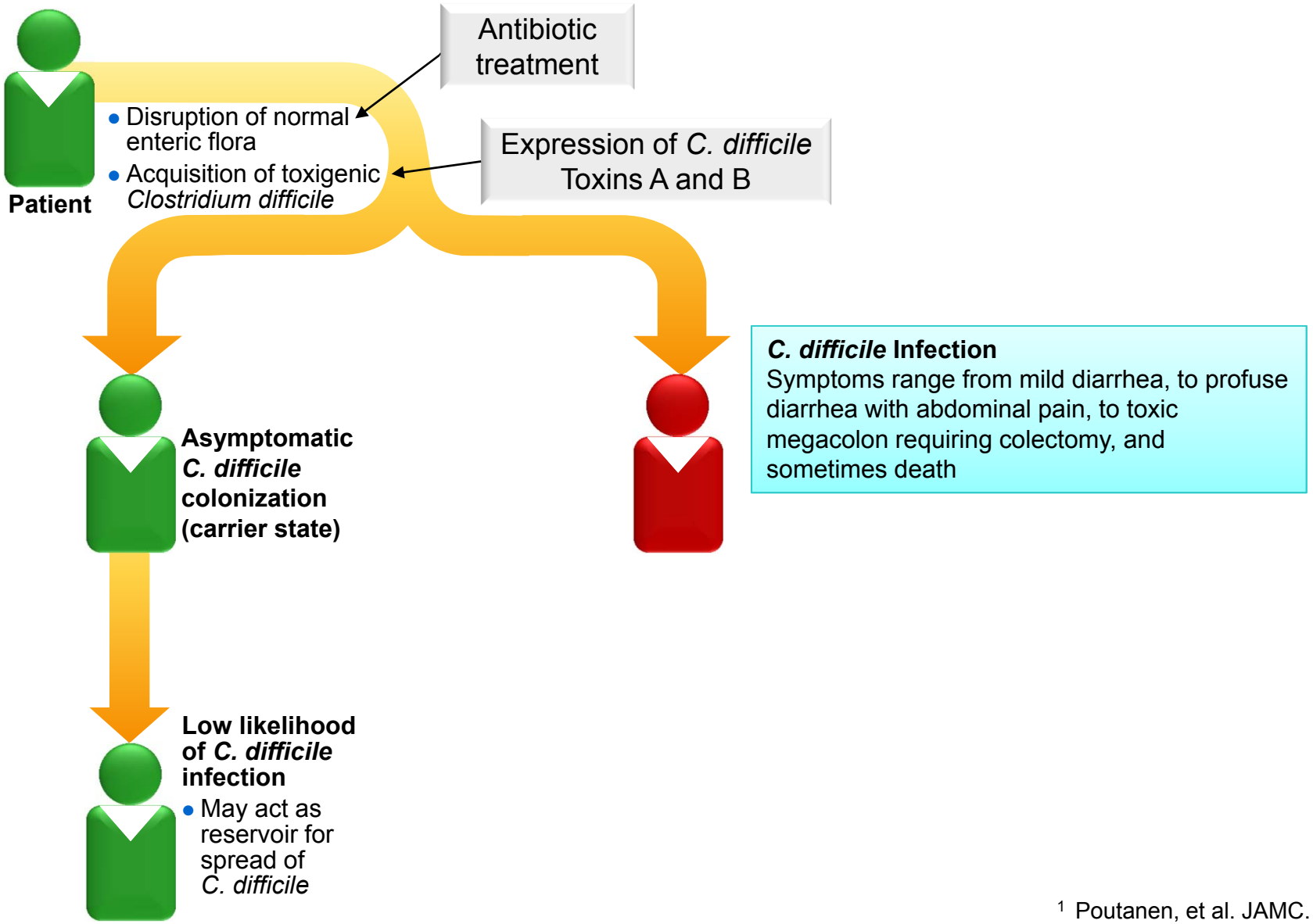
- Standard of care (SoC) treatment of CDI includes:
  - Oral/IV metronidazole
  - Oral vancomycin
  - Oral fidaxomicin
- Antibiotic treatment of CDI does not prevent recurrent disease
  - Antibiotic treatment with metronidazole or vancomycin disrupts normal gut microbiota, which facilitates development of CDI recurrence
  - CDI recurs at a substantial rate after fidaxomicin as well, in particular in those infected with the ribotype 027 (NAP1/BI)
- There are no approved therapies for the prevention of CDI recurrence

# CDI Pathogenesis[1]



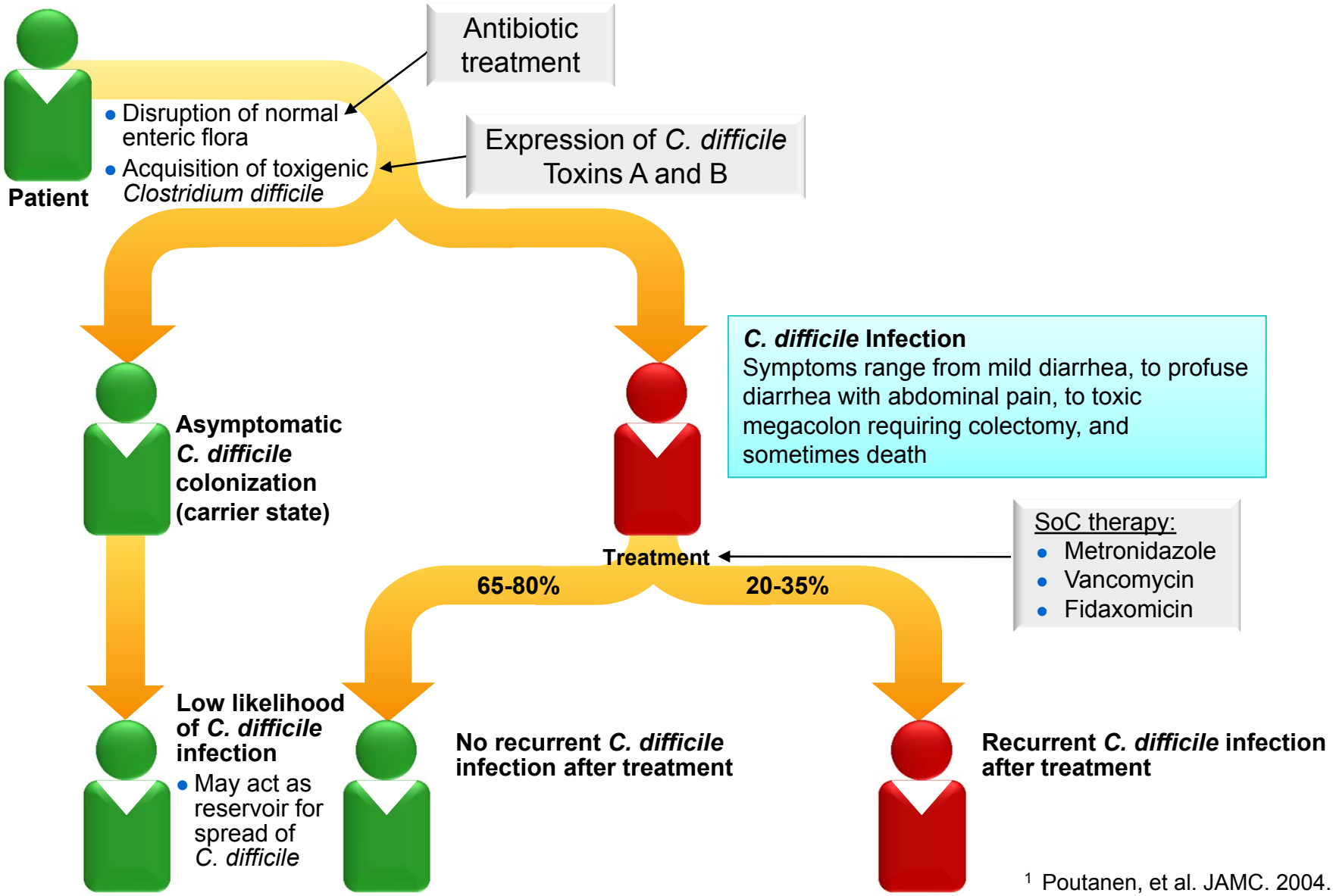

[1] Poutanen, et al. JAMC. 2004.

# CDI Pathogenesis[1]



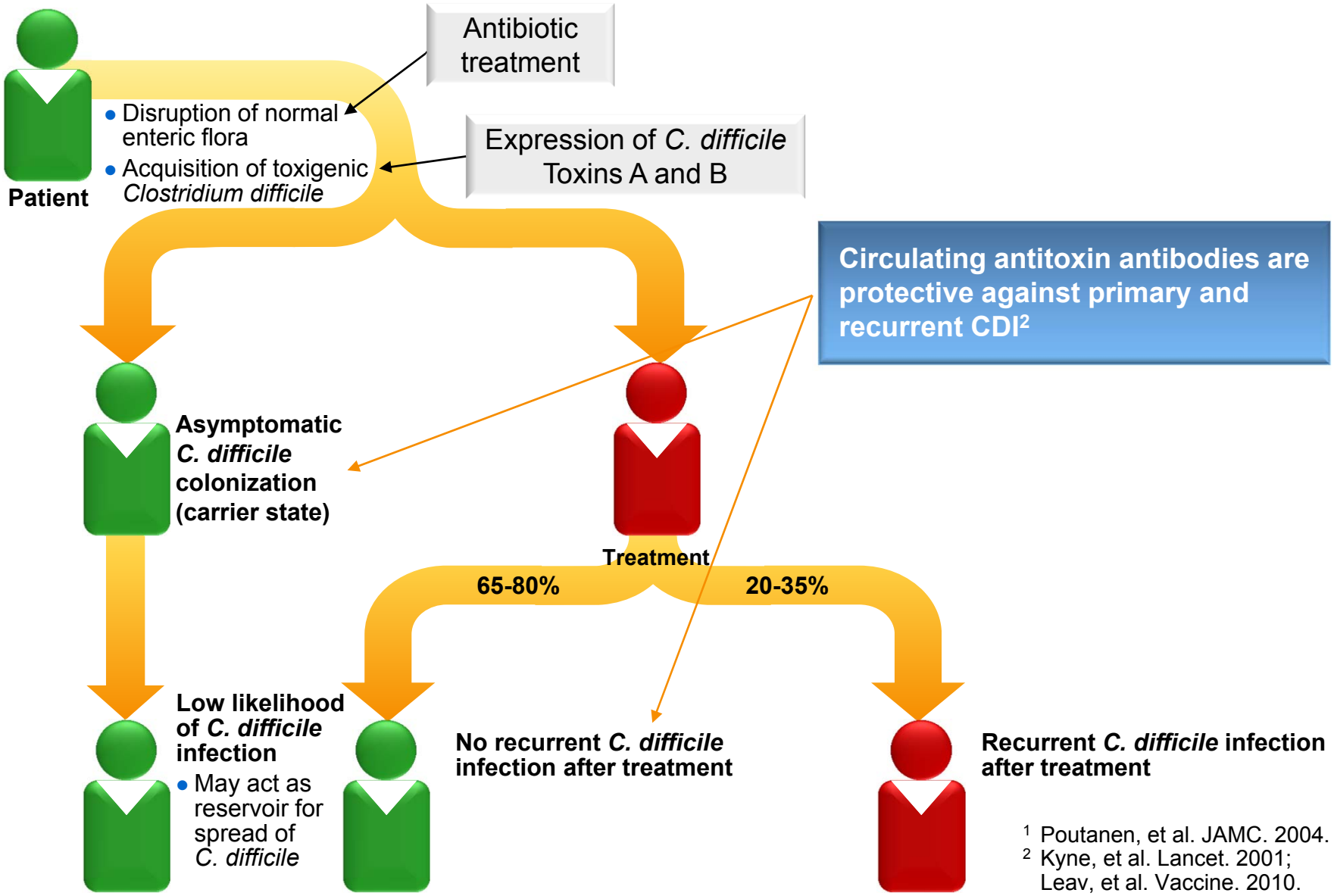

[1] Poutanen, et al. JAMC. 2004.

# CDI Pathogenesis[1]




[1] Poutanen, et al. JAMC. 2004.

# CDI Pathogenesis[1]



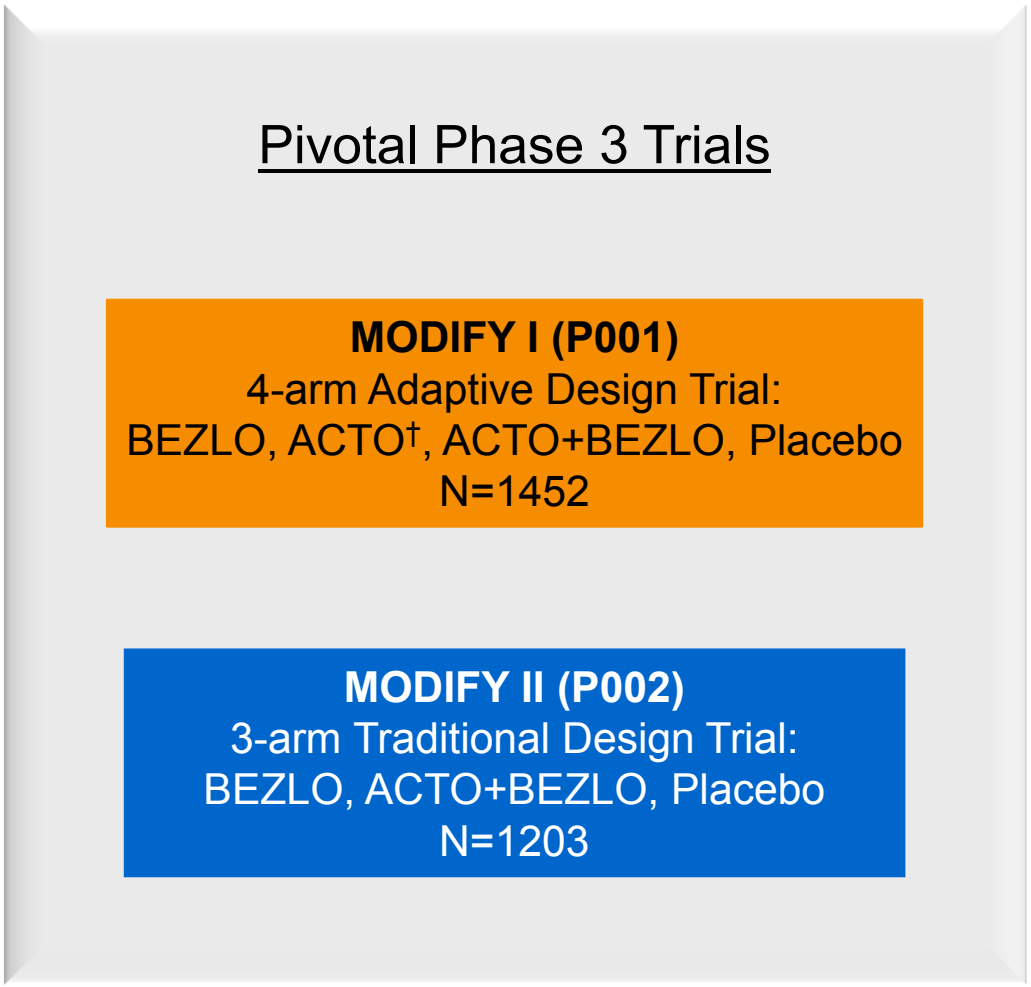

[1] Poutanen, et al. JAMC. 2004.
[2] Kyne, et al. Lancet. 2001; Leav, et al. Vaccine. 2010.

# Introduction: Bezlotoxumab

- Novel approach to the prevention of CDI recurrence
- Immune responses against toxins A/B are correlated with reduced recurrence of CDI[1]
- **Bezlotoxumab** (BEZLO, MK-6072):
  - Fully human IgG1 monoclonal antibody (mAb) that neutralizes *C. difficile* toxin B
  - Directed to the C-terminus ligand binding region of toxin B
  - Evaluated alone and in combination† with actoxumab (ACTO, MK-3415)
    - ACTO: fully human mAb targeting toxin A

[1] Kyne, et al. Lancet. 2001; Leav, et al. Vaccine. 2010.
† ACTO+BEZLO (MK-3415A): combined administration of ACTO and BEZLO.

# Bezlotoxumab Phase 3 Clinical Program




† ACTO treatment arm was discontinued after interim analysis.

# Bezlotoxumab: Phase 3 Results

- **Efficacy:** a single dose is highly efficacious in preventing CDI recurrence, significantly decreasing the proportion of subjects with CDI recurrence by 10% compared to placebo, corresponding to a ~40% reduction in relative risk

| Trial | Absolute Difference in CDI Recurrence Rate (BEZLO – Placebo) |
|---|---|
| MODIFY I | -10.1% (95% CI -15.9, -4.3), p=0.0003* |
| MODIFY II | -9.9% (95% CI -15.5, -4.3), p=0.0003* |
| MODIFY I + II (integrated) | -10.0% (95% CI -14.0, -6.0), p<0.0001* |

- **Safety:** well tolerated with a safety profile similar to placebo
- **Benefit/Risk:** overall positive benefit/risk profile

* One sided p-value.

# Proposed Indication and Dosage and Administration

- Proposed indication:
  - Bezlotoxumab is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI

- Dosage and administration:
  - The recommended dose of bezlotoxumab is 10 mg/kg administered as an intravenous infusion over 60 minutes as a single dose

# Bezlotoxumab Regulatory History

- End of Phase 2 meeting (October 2009)
  - Agreement with definition and timepoint of assessment of primary efficacy endpoint of CDI recurrence for Phase 3 trials
- Fast Track Designation granted (May 2010)
- Special Protocol Assessment (SPA) for MODIFY I (December 2010)
  - Agreement that implementation of a four-arm factorial design addresses the Combination Drug Product Rule (21 CFR 300.50)
- FDA recommended that the primary efficacy endpoint in MODIFY II be changed to global cure (August 2012)
  - Merck maintained CDI recurrence as primary endpoint and added sensitivity analyses to assess impact of clinical cure on CDI recurrence
- BLA submitted for review (November 2015)
  - Priority review designation granted (January 2016)

BLA=Biologics Licensing Application.

# Merck Consultants

| | |
|---|---|
| Ciaran P. Kelly, MD | Professor of Medicine<br>Beth Israel-Deaconess Medical Center and<br>Harvard Medical School, Boston, MA |
| Gary Koch, PhD | Professor of Biostatistics<br>University of North Carolina – Chapel Hill<br>School of Public Health, Chapel Hill, NC |
| Mark H. Wilcox, MD, FRCPath | Professor of Medical Microbiology<br>Leeds Teaching Hospitals &<br>University of Leeds<br>Lead on *C. difficile,* Public Health England |
| Janet Wittes, PhD | Founder and President<br>Statistics Collaborative, Inc. |

# Clinical Program: Overview and Efficacy

Dalya Guris, MD, MPH

*Executive Director, Bezlotoxumab Development*
*Infectious Disease Clinical Research*
*Merck Research Laboratories*

# Bezlotoxumab: Mechanism of Action

- Initial CDI episode, patient receives:
  - SoC antibiotics
  - BEZLO
- CDI resolves due to SoC antibiotics
- Outgrowth or newly-acquired *C. difficile* spores – risk of recurrence

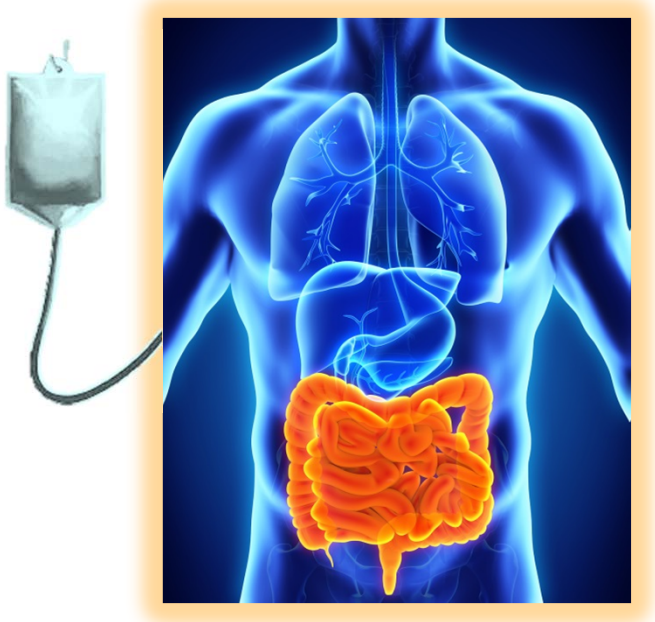


Image taken from www.nicabm.com

# Bezlotoxumab: Mechanism of Action

- Initial CDI episode, patient receives:
  - SoC antibiotics
  - BEZLO
- CDI resolves due to SoC antibiotics
- Outgrowth or newly-acquired *C. difficile* spores – risk of recurrence

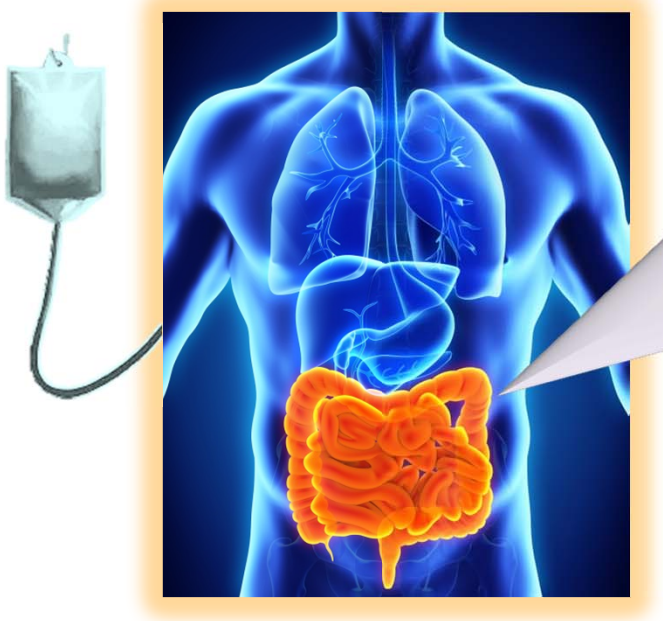
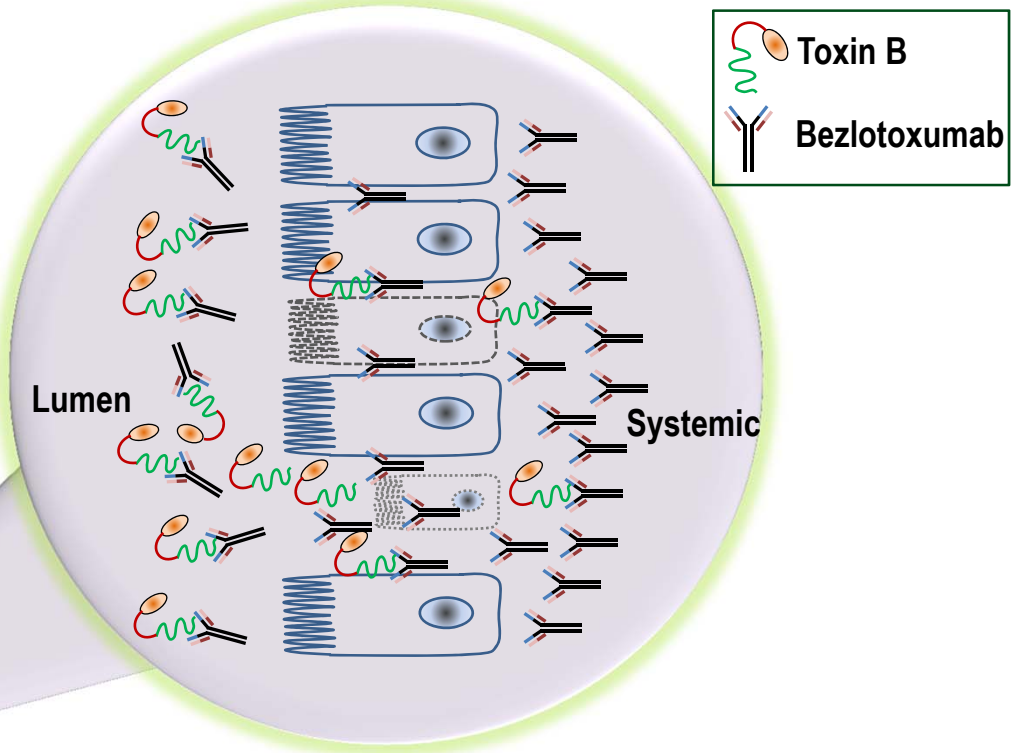


Image taken from www.nicabm.com




- Systemic BEZLO enters gut lumen via paracellular transport, facilitated by toxin
- BEZLO blocks toxin binding to mucosal cells, prevents gut wall damage/inflammation
- Long half-life of BEZLO allows sustained toxin neutralization throughout at-risk recurrence period
- Gut microbiota recovers

# Bezlotoxumab Properties

- Bezlotoxumab is a fully human monoclonal antibody (mAb) specific for an exogenous toxin (toxin B)
  - Administered as a single 10 mg/kg IV infusion over 1 hour
  - No off-target activity is expected
  - Potential for immunogenicity is low
- Pharmacokinetics (PK) similar to other fully human mAbs
  - Eliminated by protein catabolism with a half-life of 19 days
  - Low drug-drug interaction potential
- No clinically meaningful PK differences between subpopulations
  - Can be given to a diverse patient population without dose adjustment

# Phase 3 Clinical Development Program

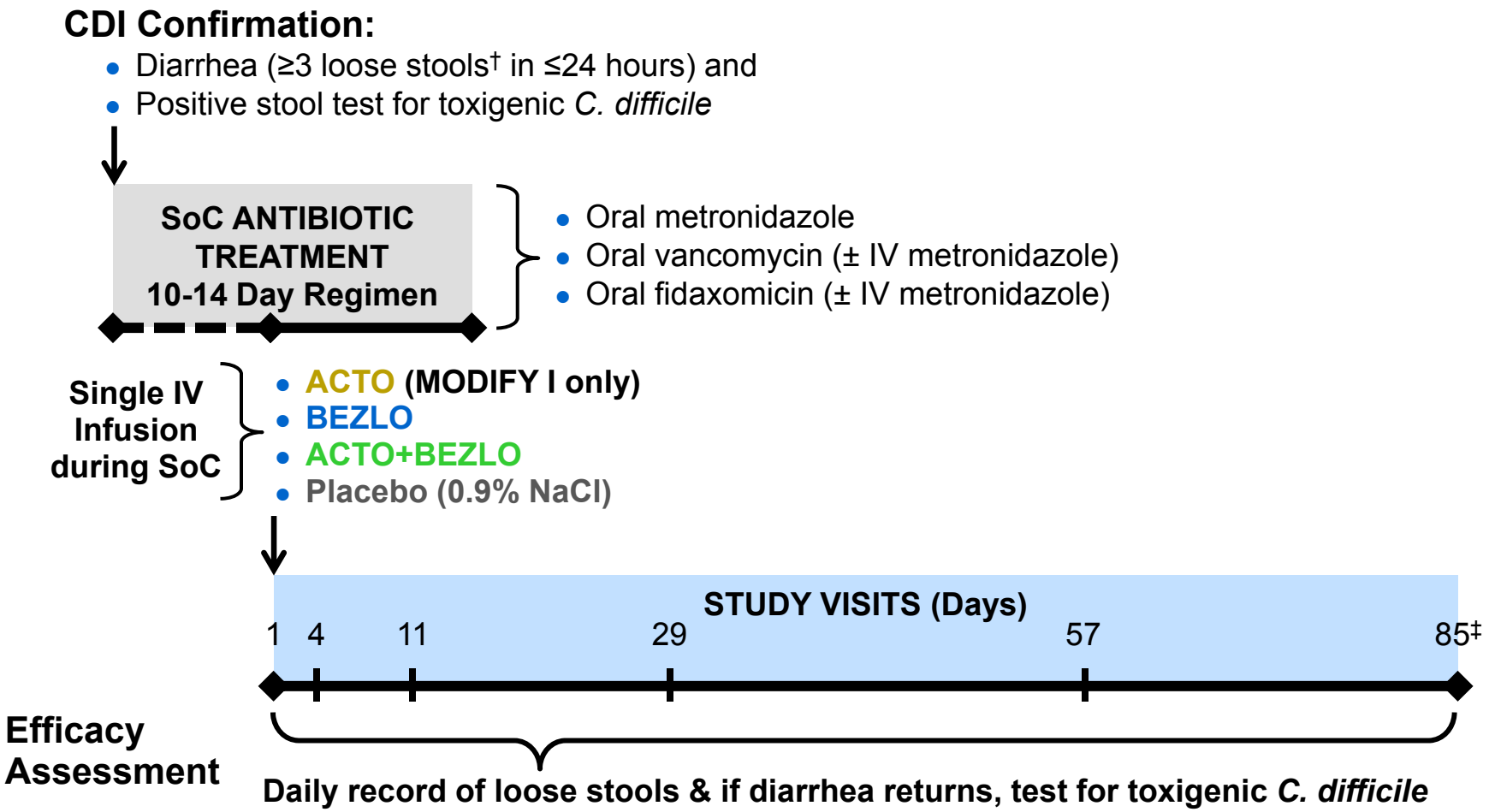
| Trial | Treatment Arms | Stratification | Planned N | Trial Design |
|---|---|---|---|---|
| MODIFY I (P001) | • **ACTO**<br>• **BEZLO**<br>• **ACTO+BEZLO**<br>• **Placebo** | • Oral SoC<br>– Metronidazole<br>– Vancomycin<br>– Fidaxomicin<br>• Hospitalization status<br>– Inpatient<br>– Outpatient | 1600 | Adaptive: one interim analysis† |
| MODIFY II (P002) | • **BEZLO**<br>• **ACTO+BEZLO**<br>• **Placebo** | | 1200 | Traditional |

† ACTO treatment arm was discontinued after interim analysis.

# MODIFY I and II: Key Inclusion/Exclusion Criteria

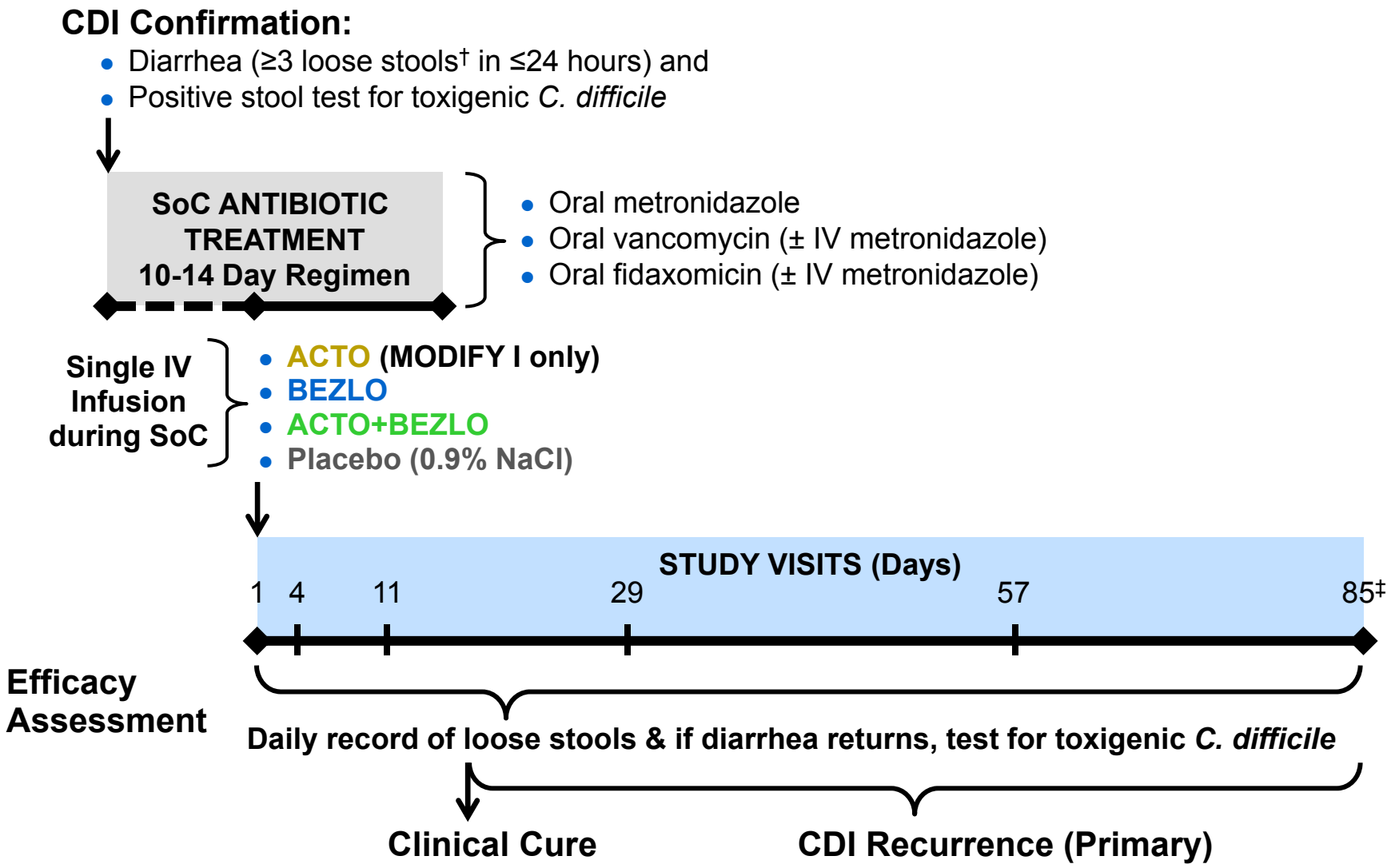
- Adult patients with confirmed *C. difficile* infection (CDI)
  - CDI confirmation based on clinical and microbiological criteria
  - Receiving SoC antibiotic therapy for CDI
- Limited exclusion criteria allowed a diverse group of CDI patients with multiple underlying co-morbidities
- Patients at high risk for CDI recurrence included
  - Elderly
  - Multiple previous episodes of CDI
  - Severe CDI
  - Immunocompromised
  - Hypervirulent strains (027, 078, 244)

# MODIFY I and II: Trial Design




† Defined by standardized Bristol Stool Chart, types 5-7.
‡ 85 days corresponds to 12 weeks.

# MODIFY I and II: Trial Design




† Defined by standardized Bristol Stool Chart, types 5-7.
‡ 85 days corresponds to 12 weeks.

# MODIFY I and II: Efficacy Endpoints

**Primary Efficacy Endpoint – CDI Recurrence**

- Definition:
  - New episode of diarrhea (≥3 loose stools in ≤24 hours) following clinical cure† of the baseline CDI episode
  - Positive local or central laboratory stool test for toxigenic *C. difficile*
- Time period: through Week 12
- Population: Full Analysis Set (FAS)

† Clinical cure:

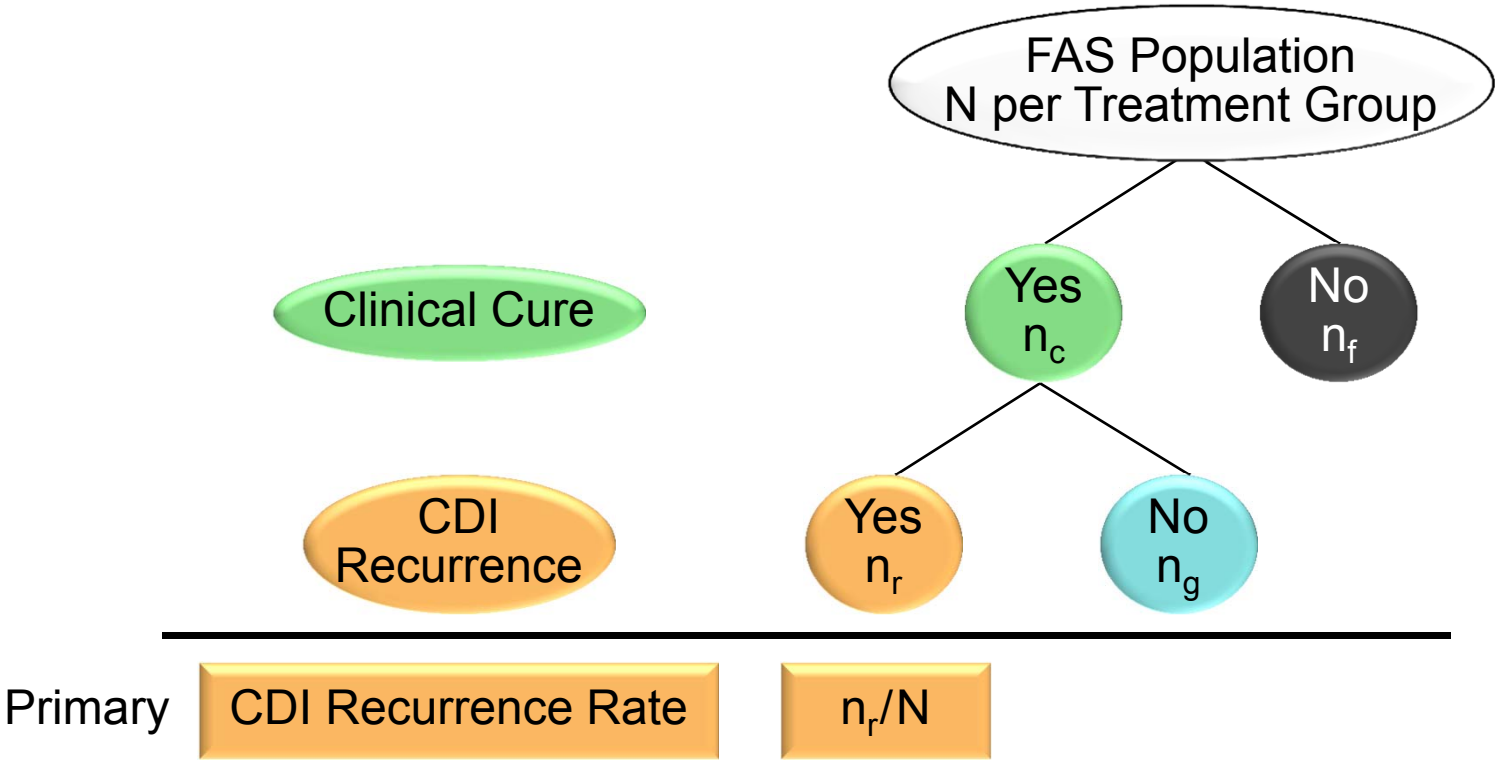
- Receipt of ≤14 day regimen (16 calendar days) of SoC antibiotic therapy, AND
- No diarrhea (≤2 loose stools per 24 hours) for the 2 consecutive days immediately after completion of SoC antibiotic therapy

# MODIFY I and II: Efficacy Endpoints

**Primary Efficacy Endpoint – CDI Recurrence**

- Definition:
  - New episode of diarrhea (≥3 loose stools in ≤24 hours) following clinical cure of the baseline CDI episode
  - Positive local or central laboratory stool test for toxigenic *C. difficile*
- Time period: through Week 12
- Population: Full Analysis Set (FAS)
  - All randomized patients, except those who
    - did not receive an infusion,
    - did not have a positive local stool test for toxigenic *C. difficile*, or
    - did not initiate protocol-defined SoC antibiotic therapy before or on the day of infusion

# MODIFY I and II: Efficacy Endpoints




FAS=full analysis set.

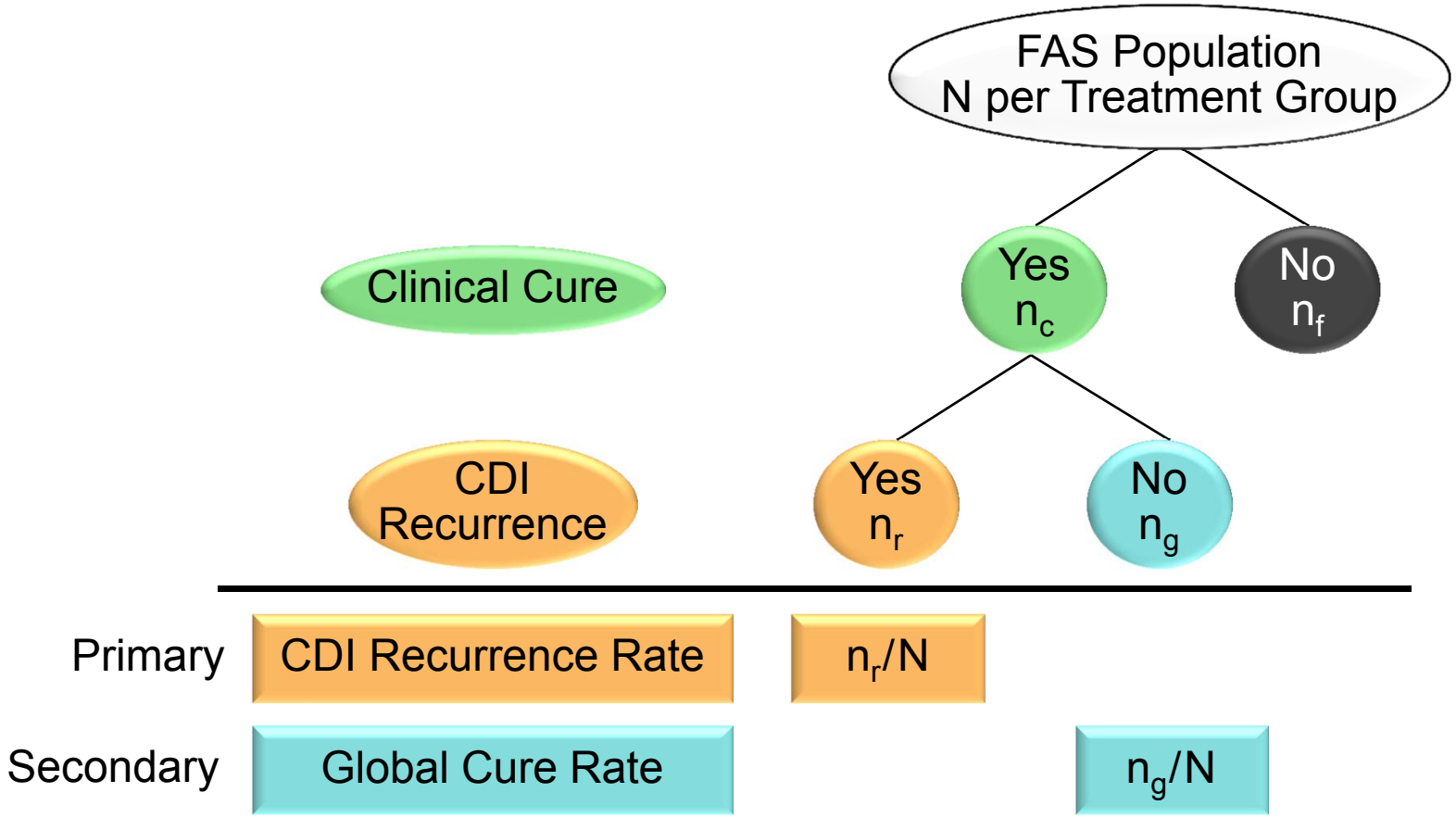
# MODIFY I and II: Efficacy Endpoints

**Global Cure (Sustained Clinical Response) – Secondary Endpoint**

- Definition: clinical cure of the initial CDI episode and no CDI recurrence
- Time period: through Week 12
- Population: FAS

FAS=full analysis set.

# MODIFY I and II: Efficacy Endpoints



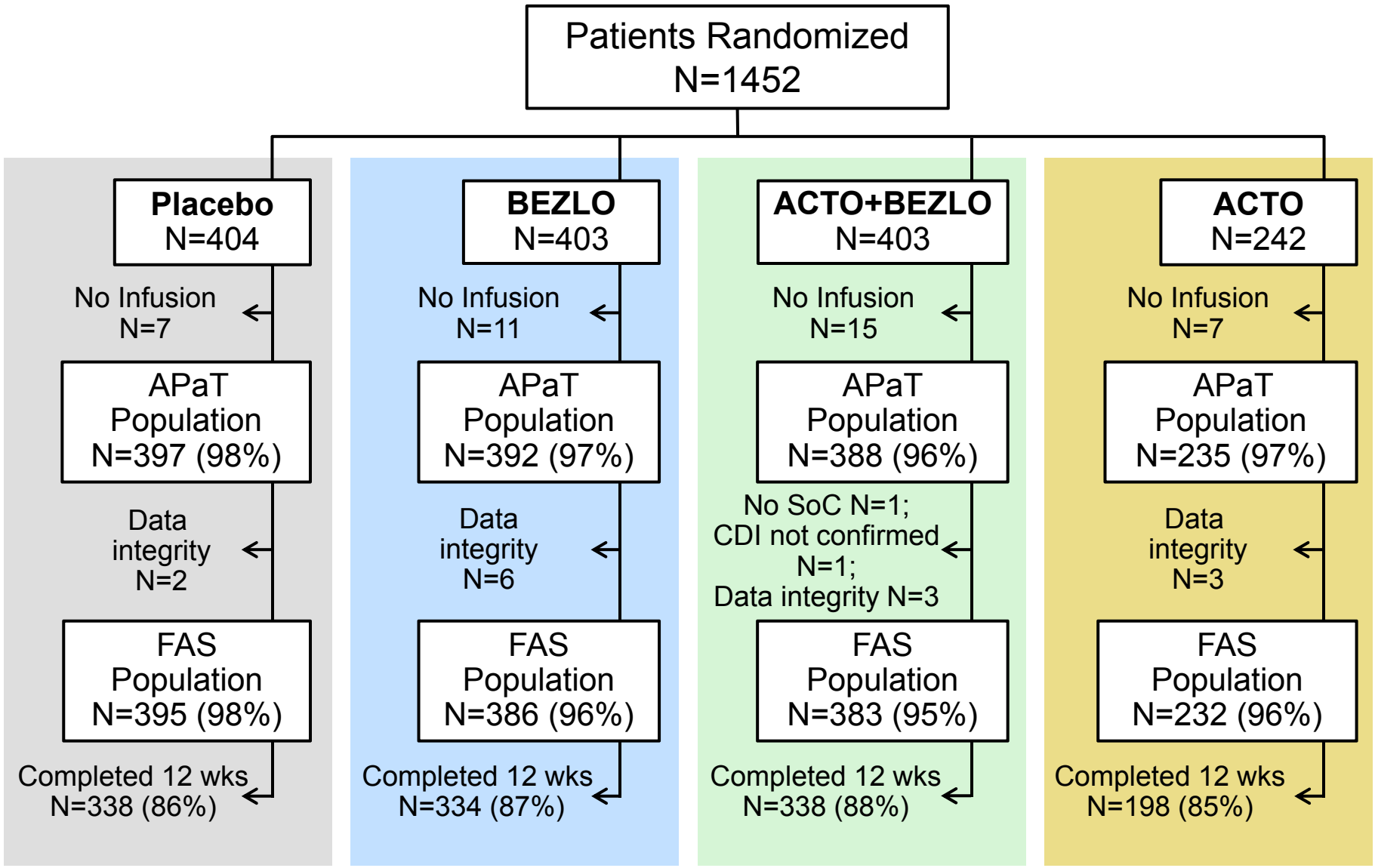

FAS=full analysis set.

# Statistical Considerations

- MODIFY I and II: two independent trials
  - Each had ≥95% power to detect an absolute difference of 8 percentage points in the rate of CDI recurrence, assuming an underlying placebo rate as low as 16%
  - Multiplicity strategy strongly controlled the study-wise Type 1 error at 0.025 (one-sided) for CDI recurrence

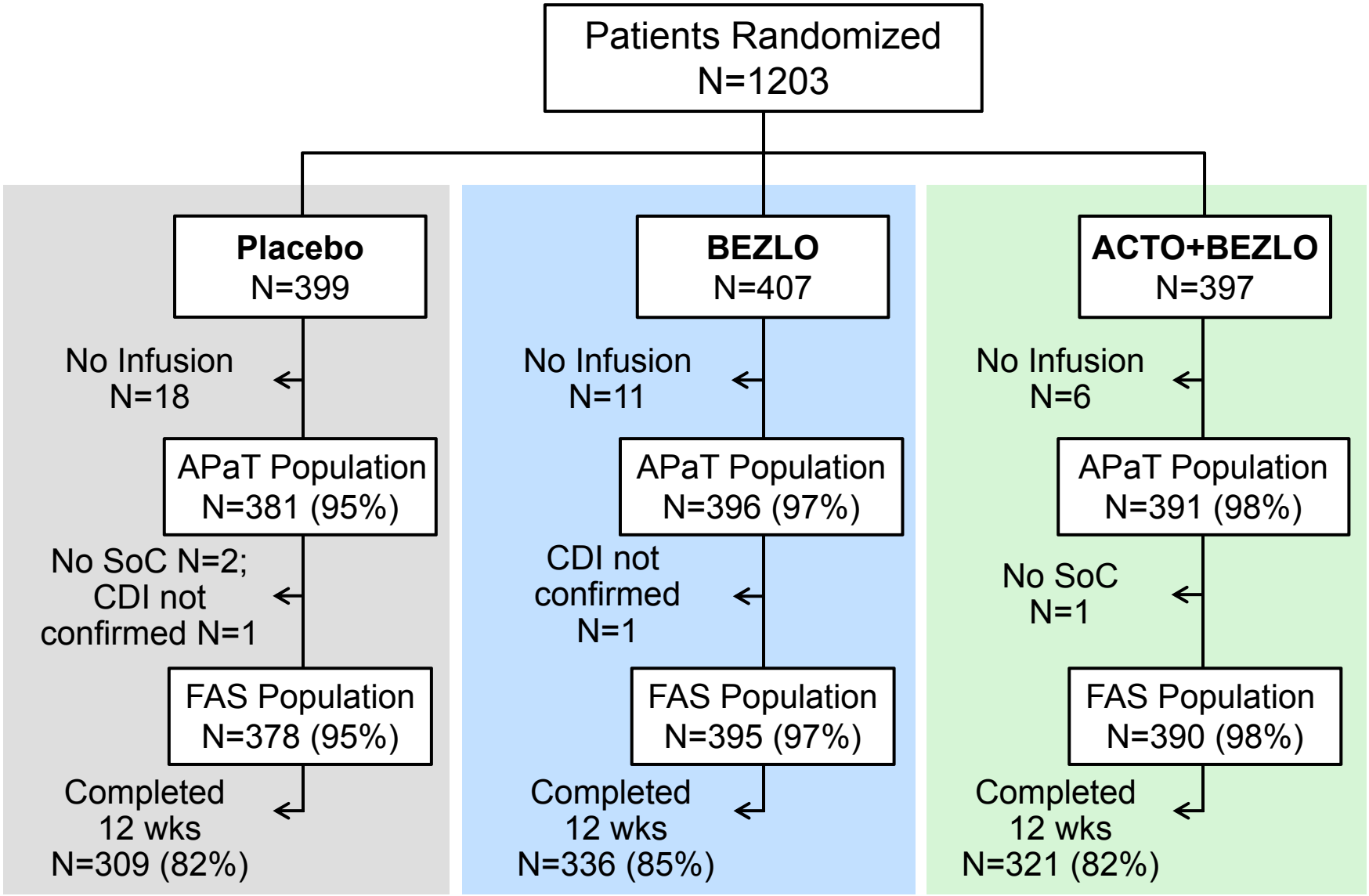
- Pre-specified integrated analyses of MODIFY I + II
  - Increased precision to estimate treatment effect of BEZLO on CDI recurrence within important subgroups and on global cure

# Study Populations – MODIFY I




APaT=all patients as treated; FAS=full analysis set.

# Study Populations – MODIFY II




APaT=all patients as treated; FAS=full analysis set.

# Baseline Characteristics
## Demographics and Stratification Factors

| | MODIFY I | | | | MODIFY II | | |
|---|---|---|---|---|---|---|---|
| | Placebo | BEZLO | ACTO+ BEZLO | ACTO | Placebo | BEZLO | ACTO+ BEZLO |
| N (FAS) | 395 | 386 | 383 | 232 | 378 | 395 | 390 |
| Age, years (Median) | 65 | 63 | 65 | 66 | 66 | 65 | 70 |
| Female, % | 56 | 59 | 55 | 56 | 60 | 54 | 54 |
| Race, % | | | | | | | |
| White | 93 | 88 | 91 | 91 | 82 | 79 | 78 |
| Black/African American | 5 | 7 | 4 | 7 | 3 | 4 | 5 |
| Asian | <1 | 1 | 1 | 1 | 15 | 16 | 17 |
| Other | 3 | 4 | 3 | 1 | 1 | 1 | 1 |
| Region, % | | | | | | | |
| North America | 53 | 51 | 53 | 57 | 42 | 40 | 41 |
| US | 47 | 44 | 46 | 52 | 35 | 34 | 34 |
| Europe | 33 | 36 | 34 | 34 | 43 | 44 | 41 |
| Asia Pacific | 6 | 5 | 4 | 4 | 14 | 15 | 16 |
| Other† | 8 | 8 | 8 | 4 | 1 | 1 | 2 |
| Inpatient‡, % | 66 | 67 | 66 | 68 | 69 | 69 | 69 |
| SoC, % | | | | | | | |
| Metronidazole | 49 | 49 | 49 | 48 | 48 | 48 | 49 |
| Vancomycin | 48 | 47 | 48 | 49 | 49 | 48 | 48 |
| Fidaxomicin | 4 | 4 | 3 | 3 | 3 | 4 | 3 |

† 'Other' region=Latin America and Africa in MODIFY I, Latin America in MODIFY II.
‡ Patients in long-term care facilities included.

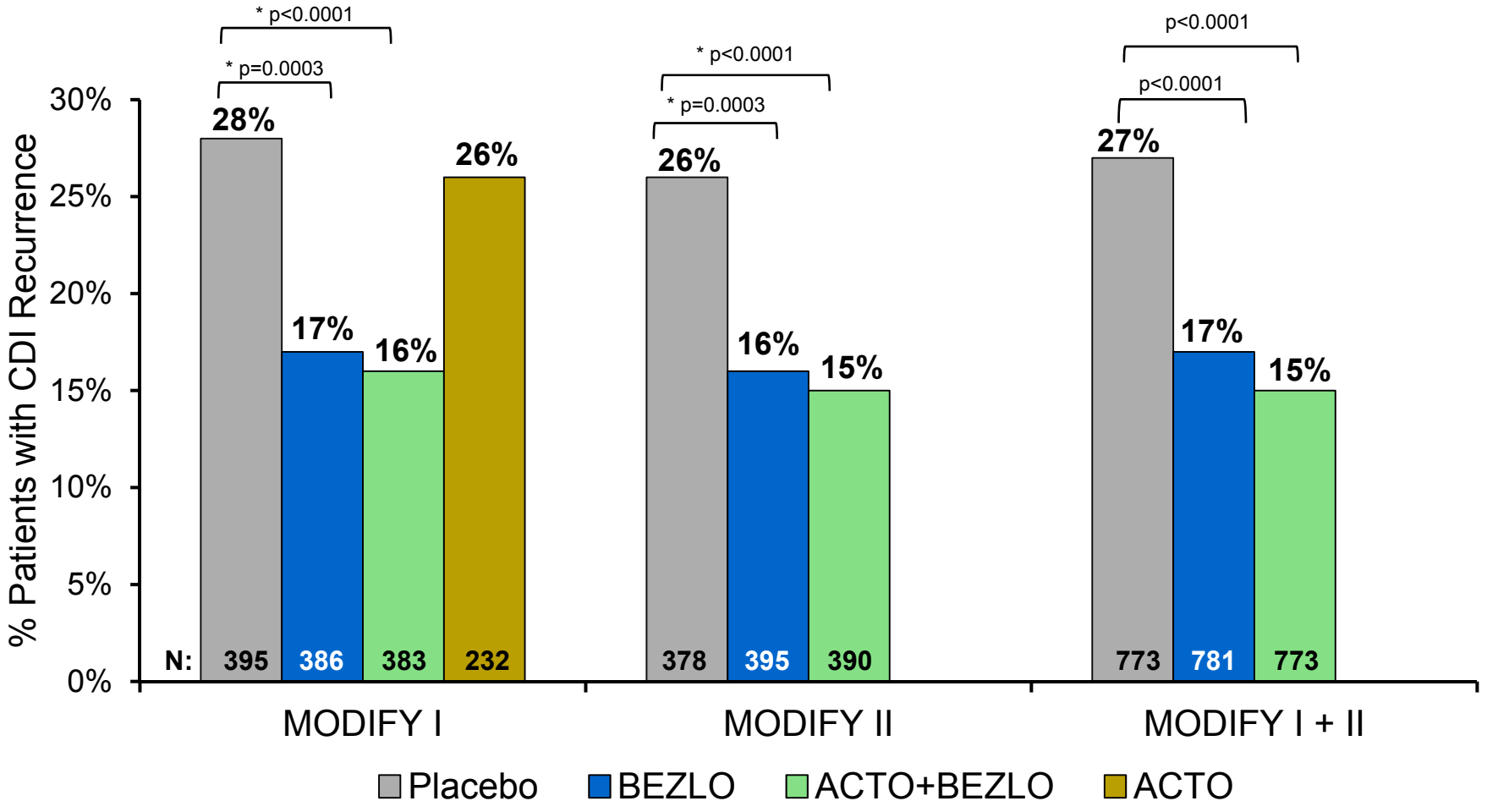
# Baseline Characteristics
## Risk Factors for CDI Recurrence

| | MODIFY I | | | | MODIFY II | | |
|---|---|---|---|---|---|---|---|
| | Placebo | BEZLO | ACTO+ BEZLO | ACTO | Placebo | BEZLO | ACTO+ BEZLO |
| N (FAS) | 395 | 386 | 383 | 232 | 378 | 395 | 390 |
| ≥65 years, % | 50 | 48 | 52 | 53 | 54 | 52 | 62 |
| ≥1 CDI in last 6 months, % | 28 | 27 | 25 | 30 | 29 | 29 | 27 |
| ≥2 CDI in the past, % | 18 | 11 | 13 | 15 | 14 | 14 | 14 |
| Severe CDI (Zar score ≥2)[1], % | 15 | 17 | 16 | 13 | 17 | 14 | 21 |
| Immunocompromised, % | 23 | 23 | 20 | 24 | 14 | 21 | 19 |
| N (FAS with *C. diff.* isolated) | 245 | 253 | 226 | 144 | 241 | 237 | 251 |
| Hypervirulent strains[†,‡], % | 18 | 20 | 19 | 21 | 30 | 22 | 18 |
| 027 strain[†], % | 15 | 18 | 16 | 17 | 27 | 18 | 16 |

- 76% of patients had at least 1 risk factor for CDI recurrence

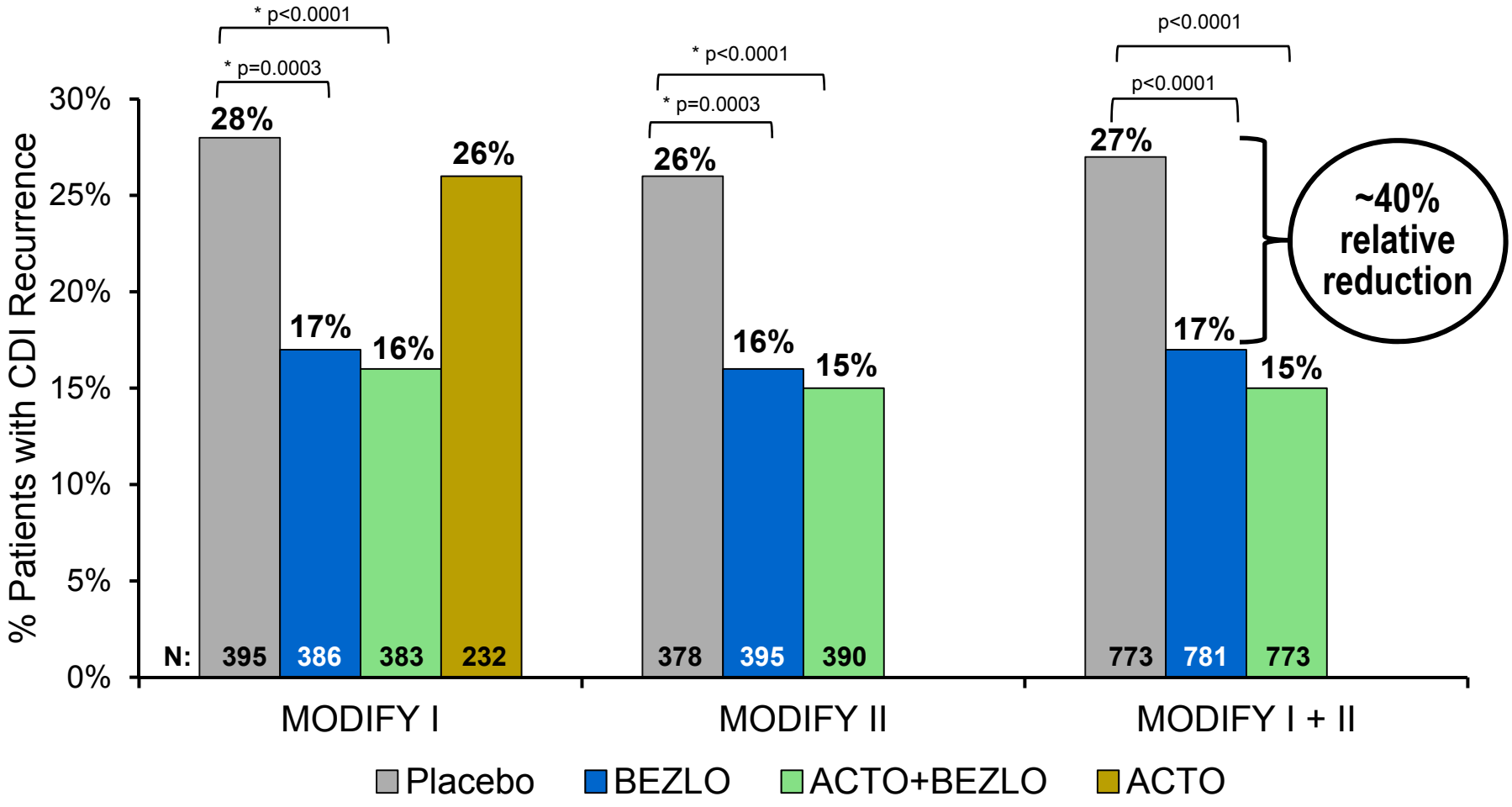
[1] Zar, et al. Clin Infect Dis. 2007.
[†] Among FAS with *C. difficile* isolated at baseline (62% of population).
[‡] Ribotypes 027, 078, 244.

# BEZLO Significantly Reduces CDI Recurrence



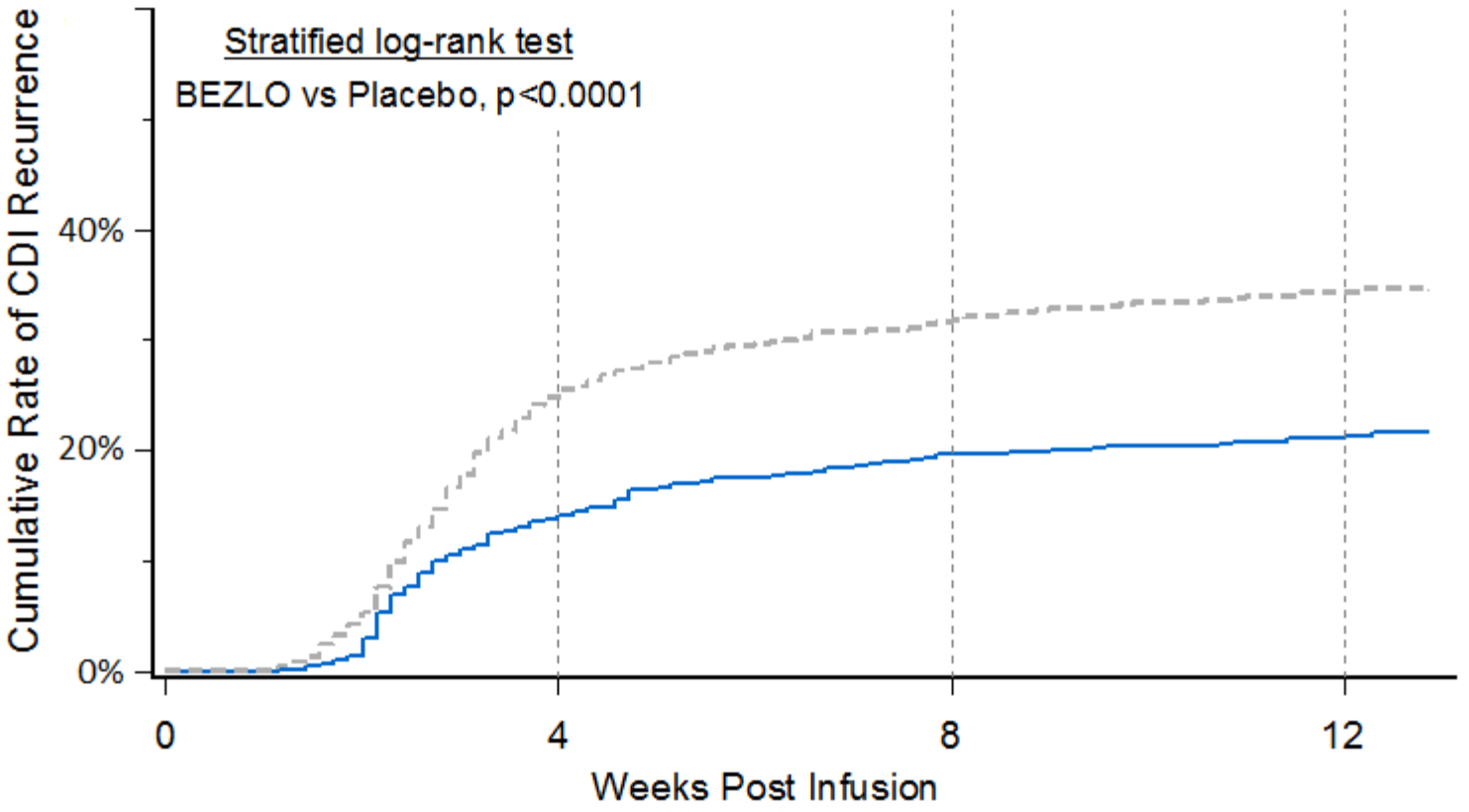

* Significantly different from placebo, after adjusting for multiplicity.
Note: p-values are one-sided.

# BEZLO Significantly Reduces CDI Recurrence




* Significantly different from placebo, after adjusting for multiplicity.
Note: p-values are one-sided.

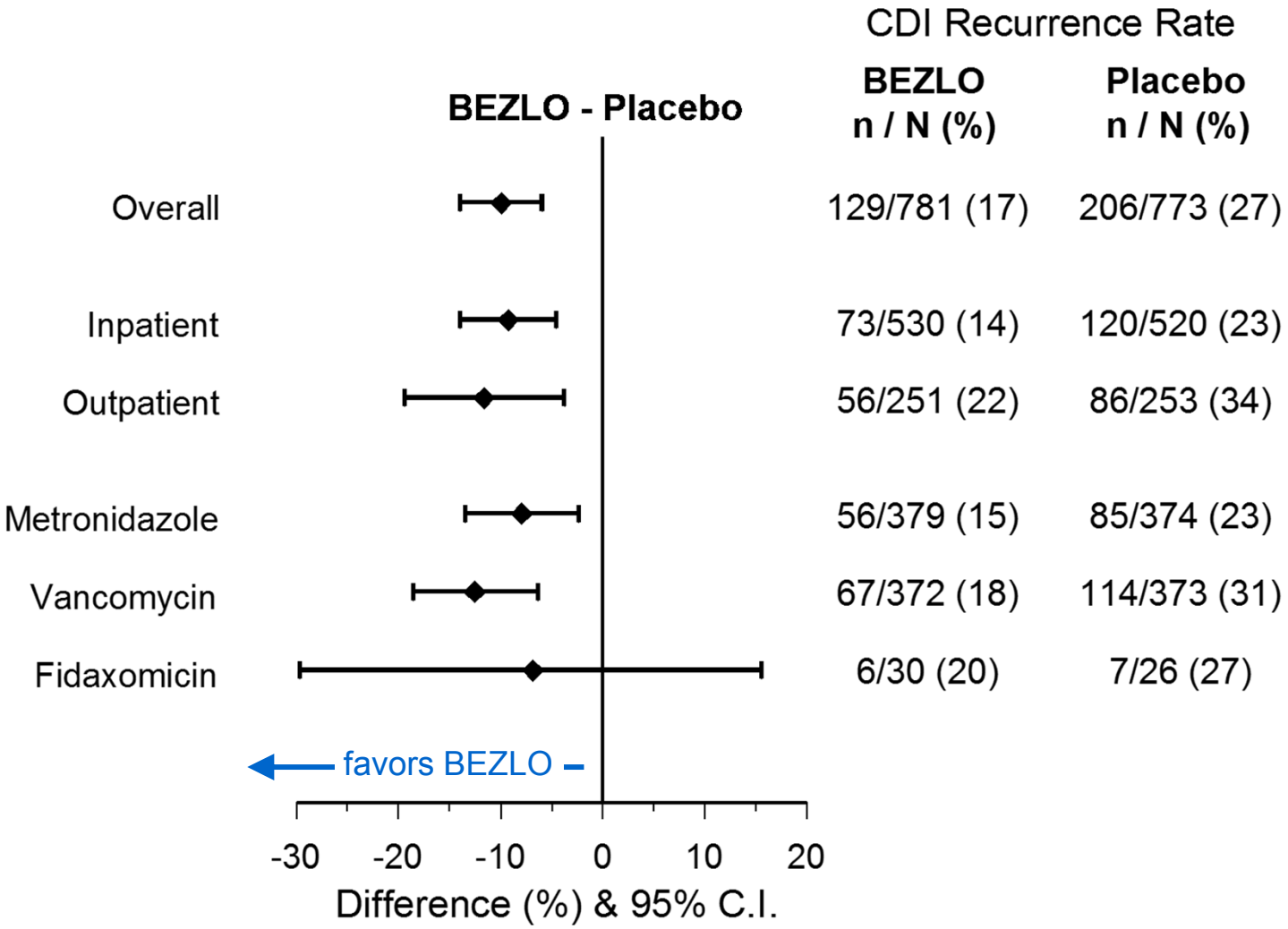
# BEZLO Reduces CDI Recurrence Through 12 Weeks, MODIFY I + II



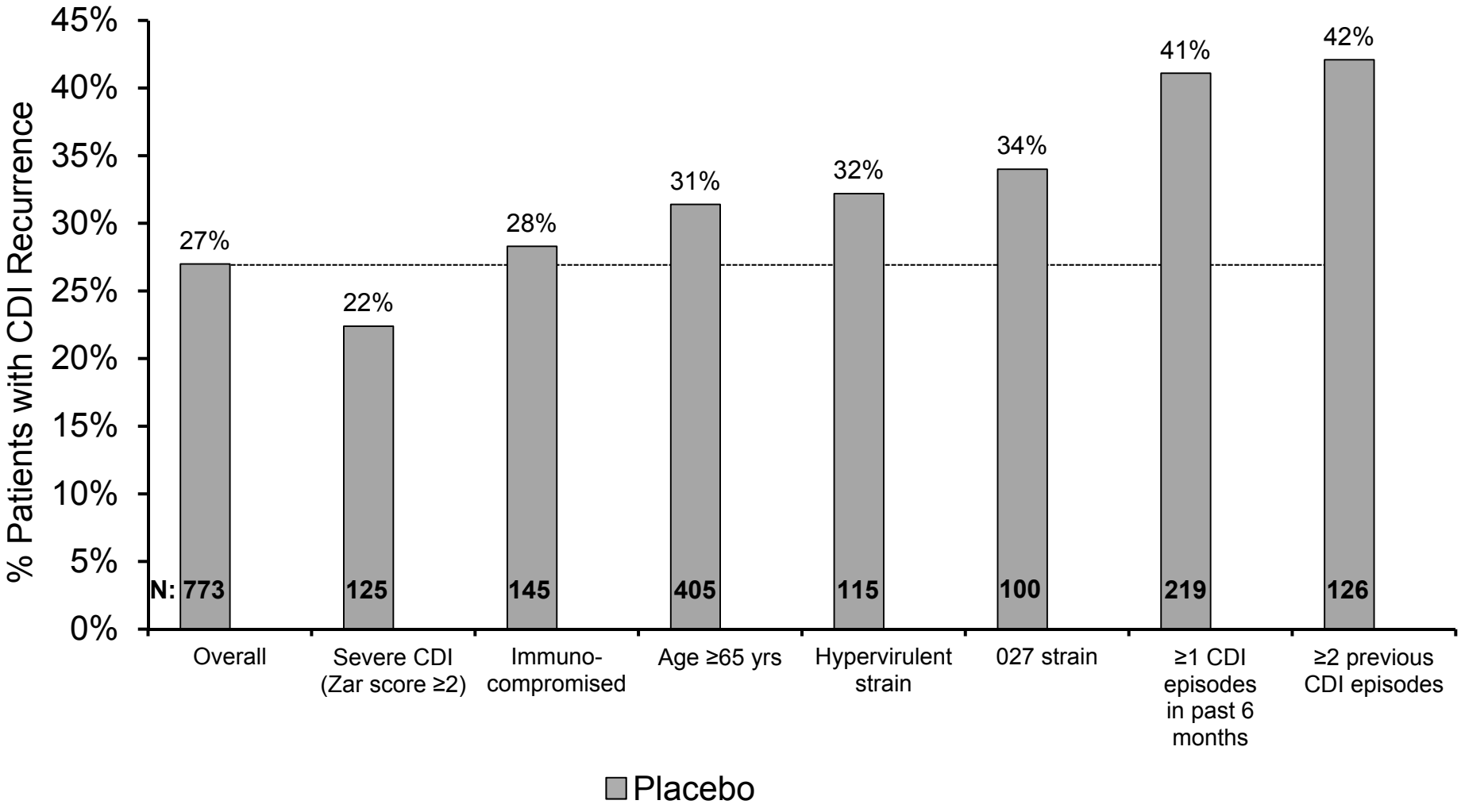

No. at Risk: Kaplan Meier Estimates (95% CI)

| | | | | |
|---|---|---|---|---|
| Placebo | 773 | 443: 25% (22, 29) | 386: 32% (28, 35) | 272: 34% (30, 38) |
| BEZLO | 781 | 518: 14% (11, 17) | 463: 20% (17, 23) | 343: 21% (18, 25) |

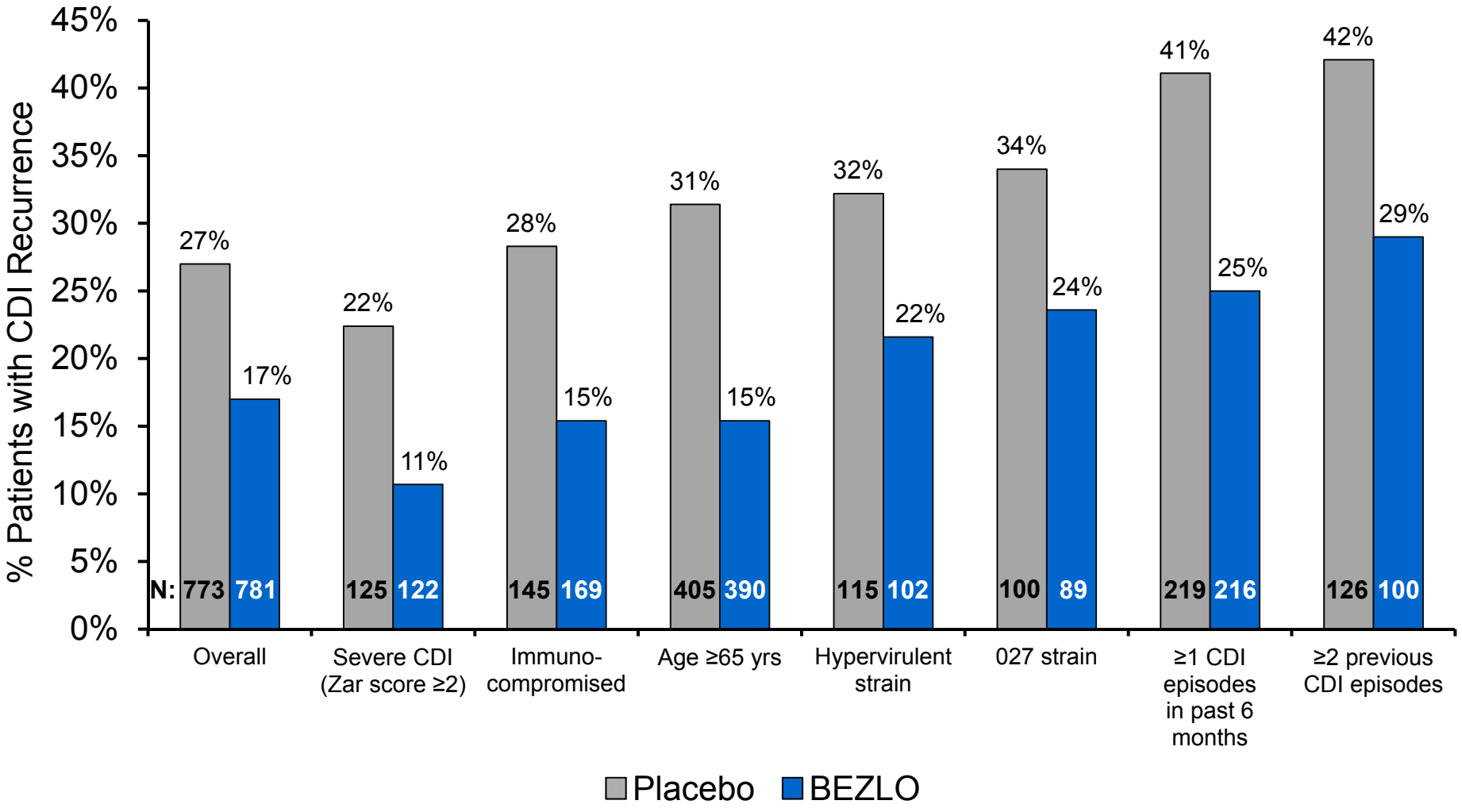
# BEZLO Reduces CDI Recurrence Across Stratification Factors, MODIFY I + II



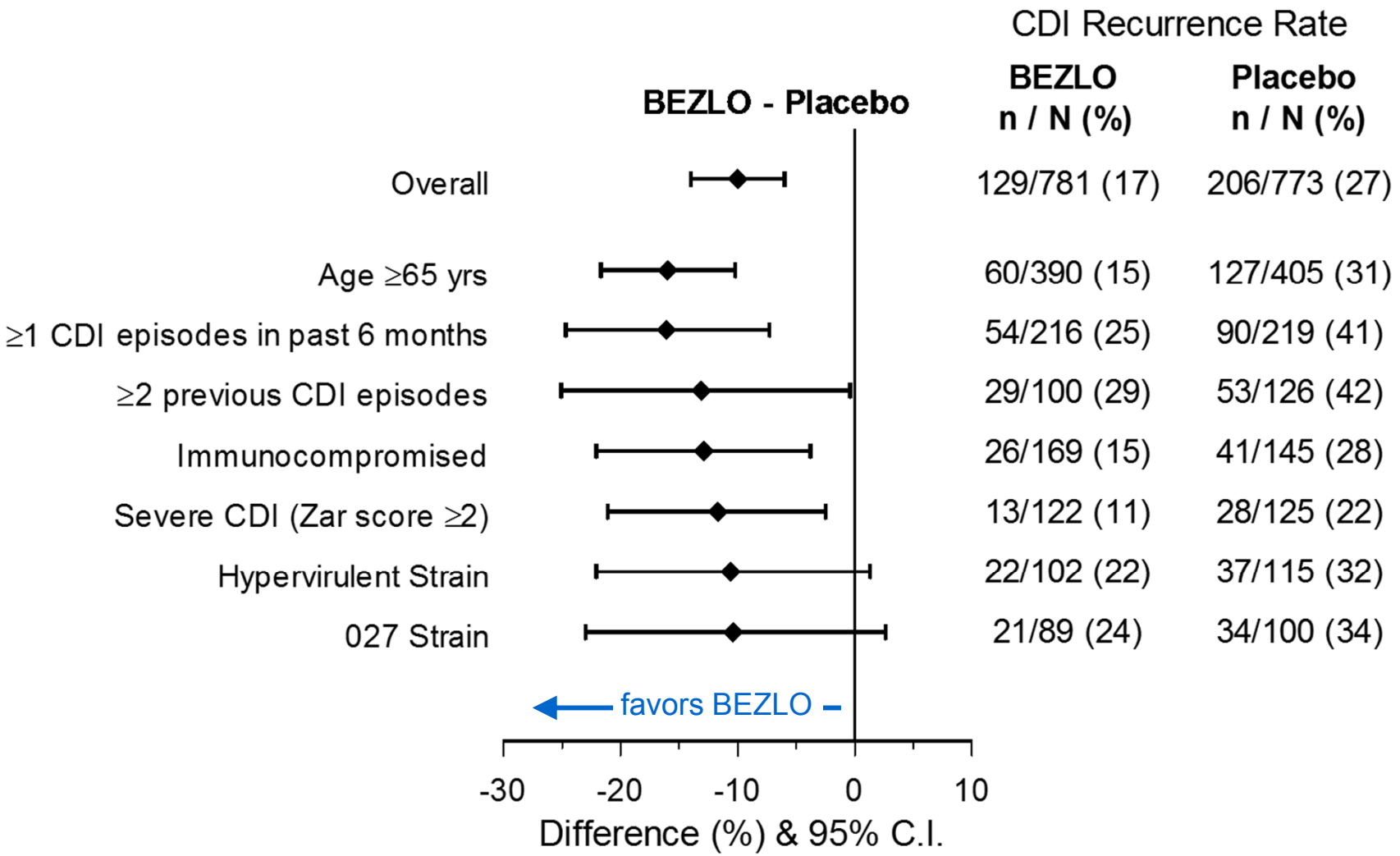
# CDI Recurrence in Subgroups in High Risk Groups, MODIFY I + II



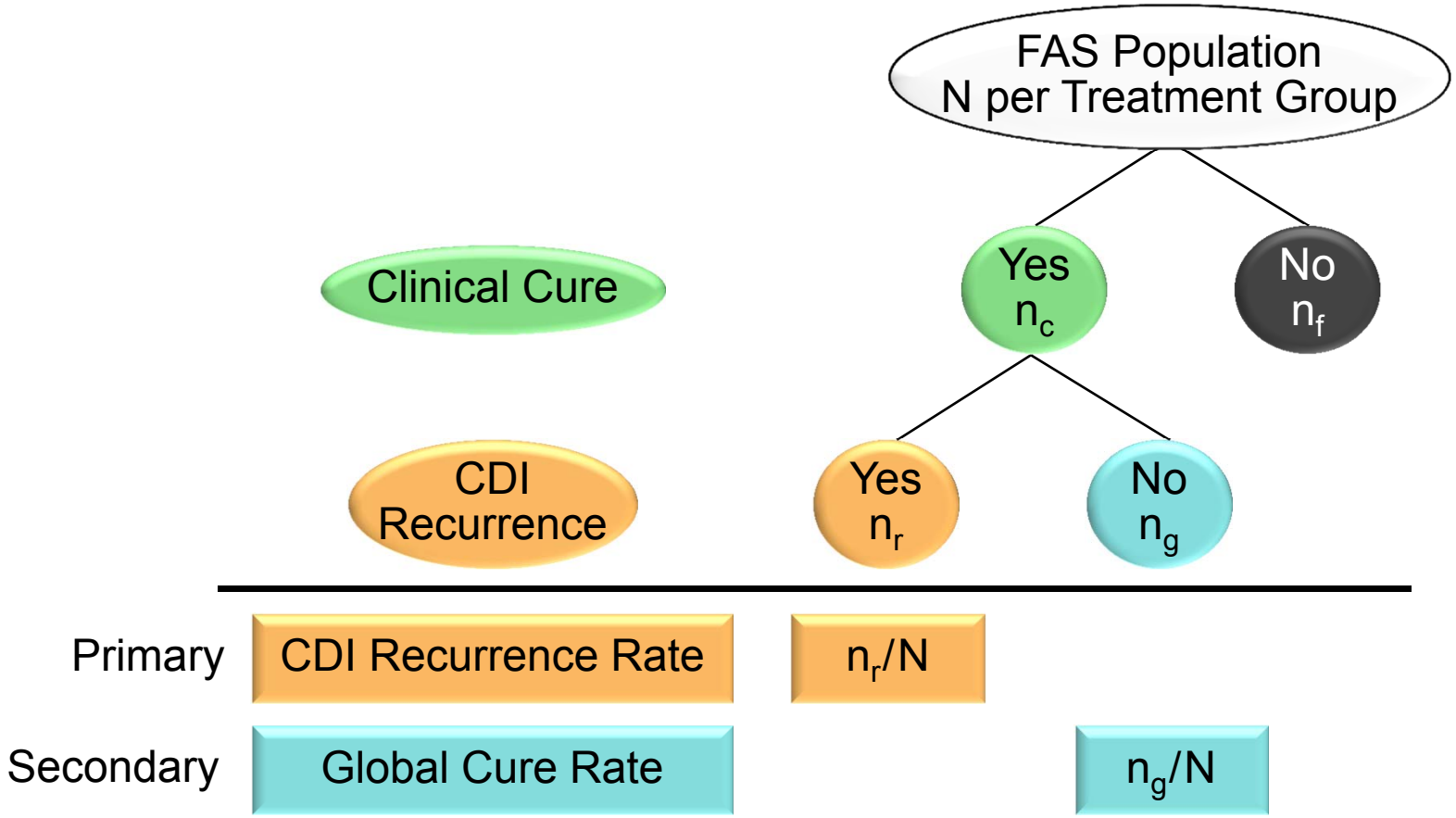
# CDI Recurrence in Subgroups in High Risk Groups, MODIFY I + II



# BEZLO Reduces CDI Recurrence in Subgroups in High Risk Groups, MODIFY I + II

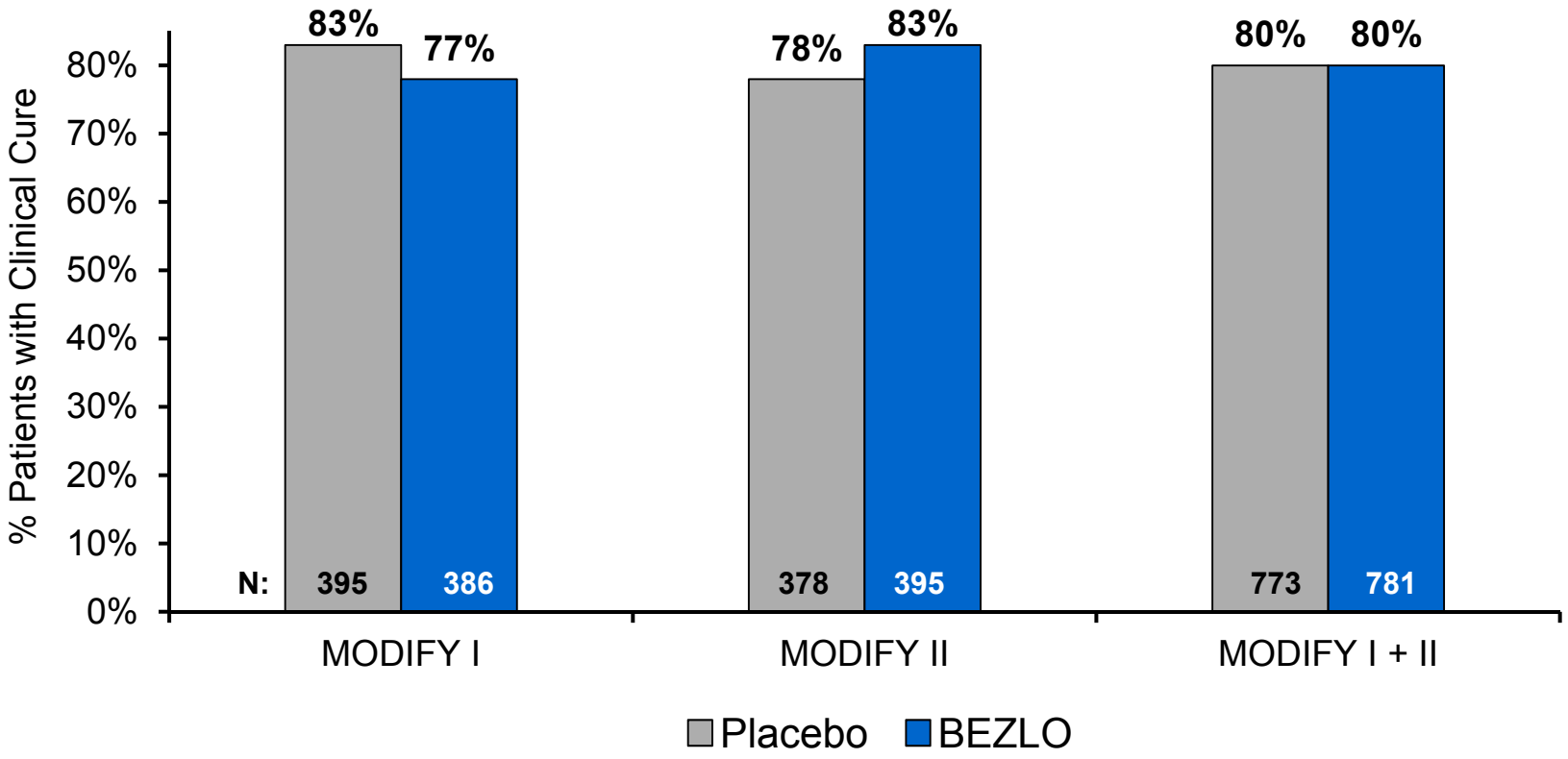


# MODIFY I and II: Efficacy Endpoints

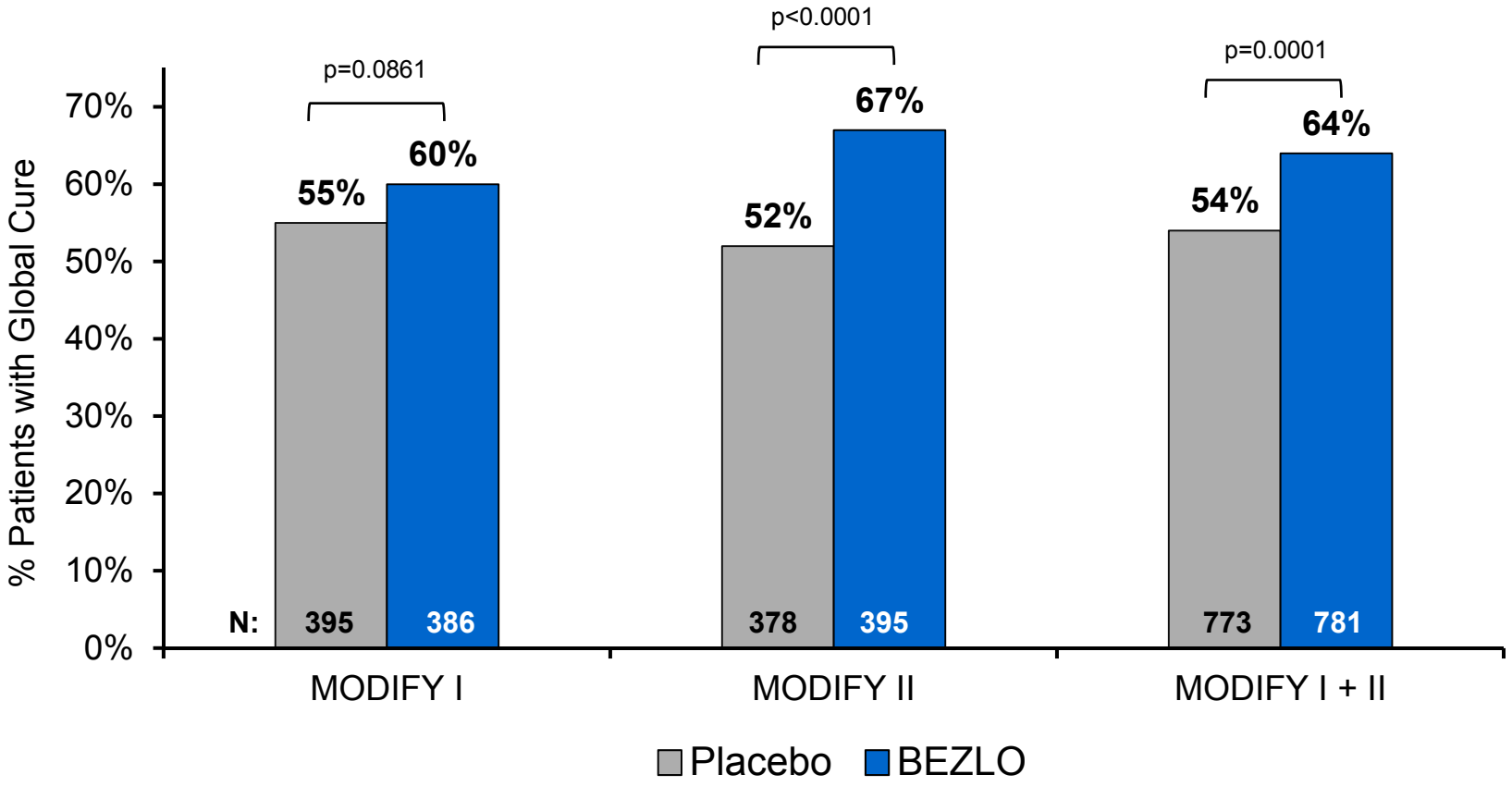



FAS=full analysis set.

# BEZLO Does Not Impact Clinical Cure Rates



# BEZLO Is Efficacious in Achieving Global Cure




Note: p-values are one-sided.

# CDI Recurrence and Global Cure Endpoints for Assessing Prevention of CDI Recurrence

| Endpoint | Advantages | Disadvantages |
|---|---|---|
| CDI Recurrence | • More appropriate measure to assess efficacy of therapy that does not treat the incident CDI episode but only prevents CDI recurrence | • Counts patients who do not achieve clinical cure as not having CDI recurrence |
| Global Cure | • More appropriate measure to assess efficacy of therapy that also treats the incident CDI episode | • Counts patients who do not achieve clinical cure as having CDI recurrence |

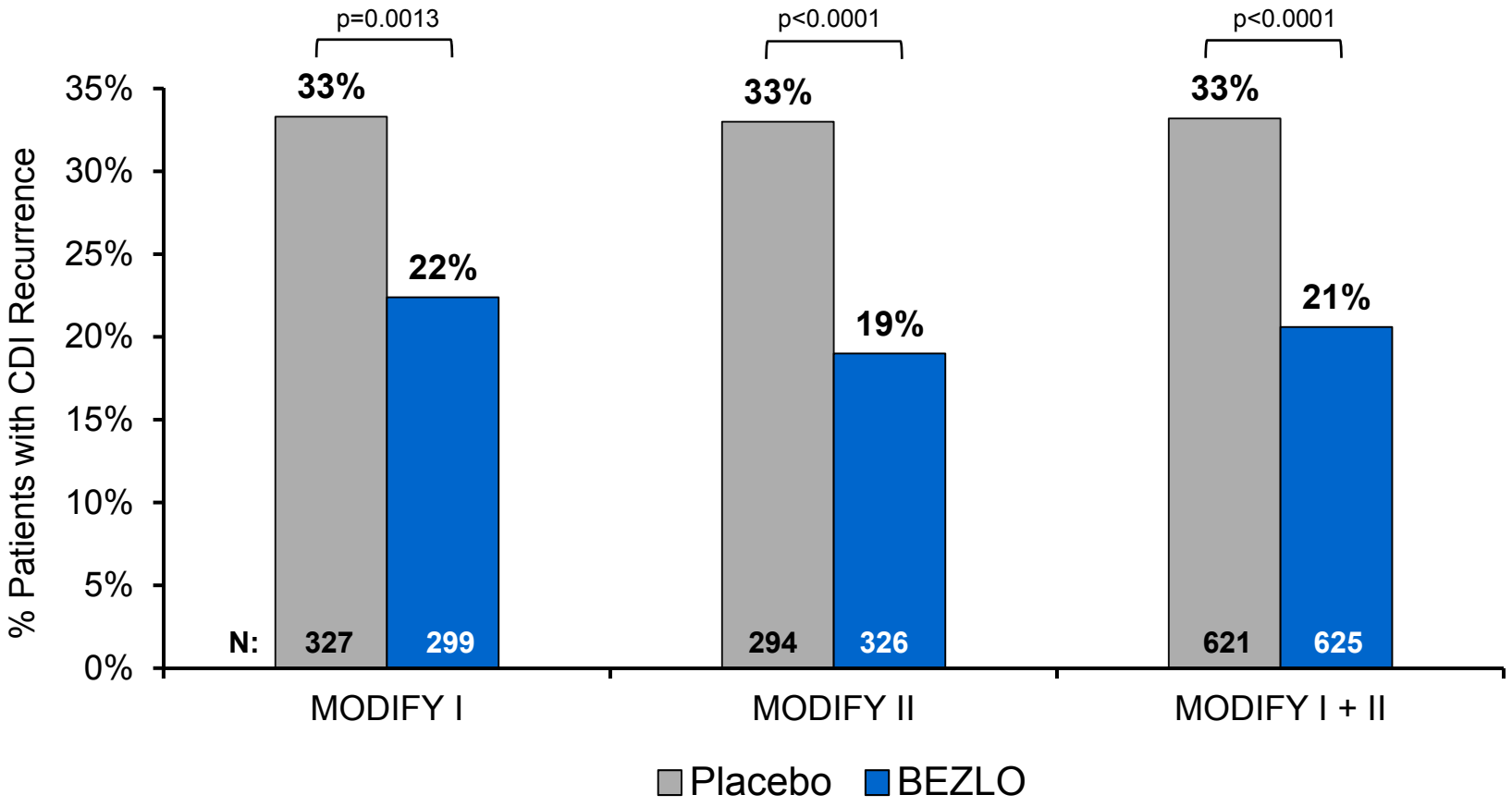
**Since BEZLO dosing was not mandated to occur at the point of clinical cure of the incident CDI episode, both the CDI recurrence and global cure endpoints are impacted by the definition of clinical cure.**

# Assessment of Robustness of Primary Efficacy Endpoint

- Sensitivity analyses assessing CDI recurrence in:
  - Clinical cure subset (secondary endpoint)
  - FAS using an expanded definition of clinical cure

- Sensitivity analyses assessing impact of incomplete data
  - Diarrhea recurrence irrespective of etiology (exploratory endpoint)
  - CDI recurrence imputing patients meeting the following criteria as having a recurrence:
    - Discontinued from study
    - Discontinued from study and/or diarrhea with no toxigenic *C. difficile* test in the follow-up period
    - Discontinued from study and/or diarrhea with no toxigenic *C. difficile* test and/or CDI-active therapy in the follow-up period

# BEZLO Reduces CDI Recurrence in the Clinical Cure Subset†




Note: p-values are one-sided.
† Denominator is the Clinical Cure subset of the FAS population.

# Protocol-Defined Clinical Cure

- Definition:
  - Receipt of ≤14 day regimen (16 calendar days) of SoC therapy

    AND
  - No diarrhea (≤2 loose stools per 24 hours) for the 2 consecutive days immediately after completion of SoC therapy

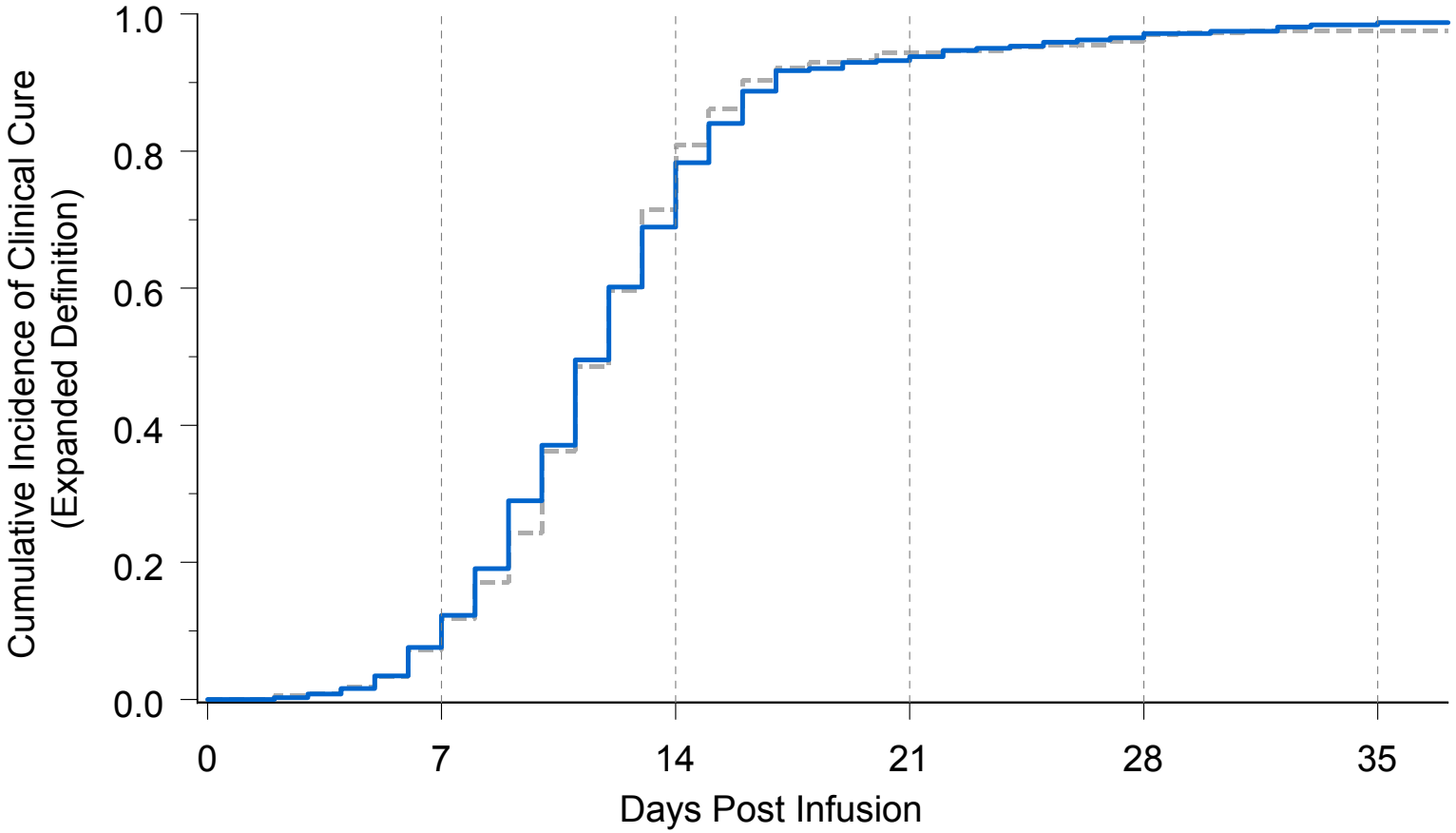
- Rationale for protocol definition of clinical cure:
  - Standardization of SoC duration and follow up period across patients

- Resulted in a larger than expected proportion of subjects failing to achieve clinical cure
  - Incidence of clinical cure was ~80% in MODIFY I + II (vs. ~90% in the fidaxomicin Phase 3 trials)
  - ~20% of patients in the MODIFY FAS population were imputed as "success" for CDI recurrence and "failure" for global cure

# Expanded Definition of Clinical Cure

- *Expanded* definition:
  - No diarrhea (≤2 loose stools per 24 hours) on 2 consecutive days after completion of any duration of SoC therapy
    - More clinically relevant definition for patients and prescribers
- Sensitivity analysis with *expanded* definition of clinical cure:
  - Minimizes the number of patients for whom CDI recurrence is imputed as a success or failure
  - Uses all *observed data* on the presence or absence of CDI recurrence

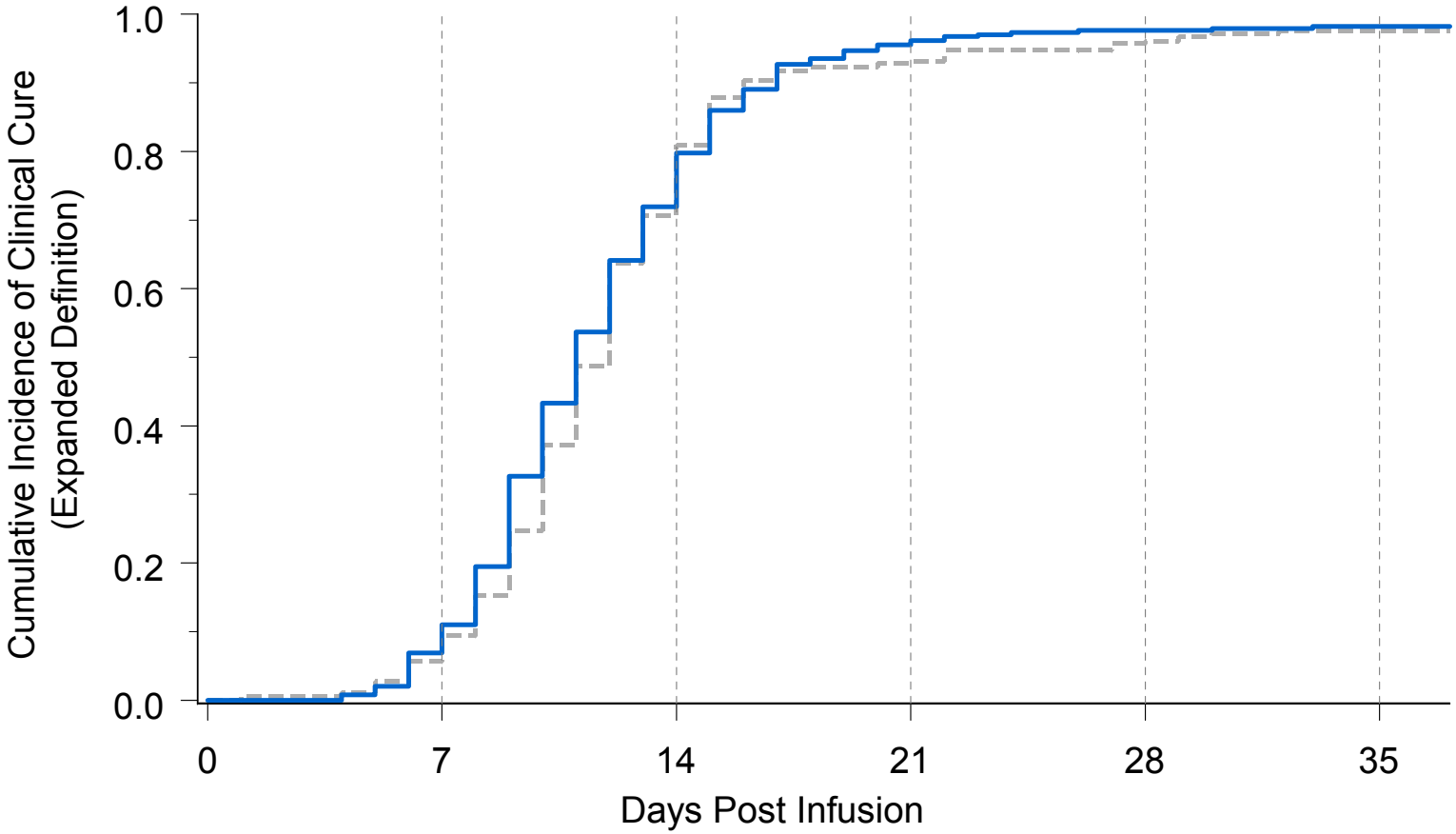
# Sensitivity Analyses: Time to Clinical Cure – Expanded Definition (MODIFY I)




No. at Risk: KM Estimates (95% CI)

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 395 | 364: 12% (9, 15) | 106: 81% (77, 85) | 20: 94% (92, 97) | 13: 97% (95, 99) | 8: 98% (96, 99) |
| BEZLO | 386 | 354: 12% (9, 16) | 116: 78% (74, 82) | 23: 94% (91, 96) | 11: 97% (95, 99) | 5: 99% (98, 100) |

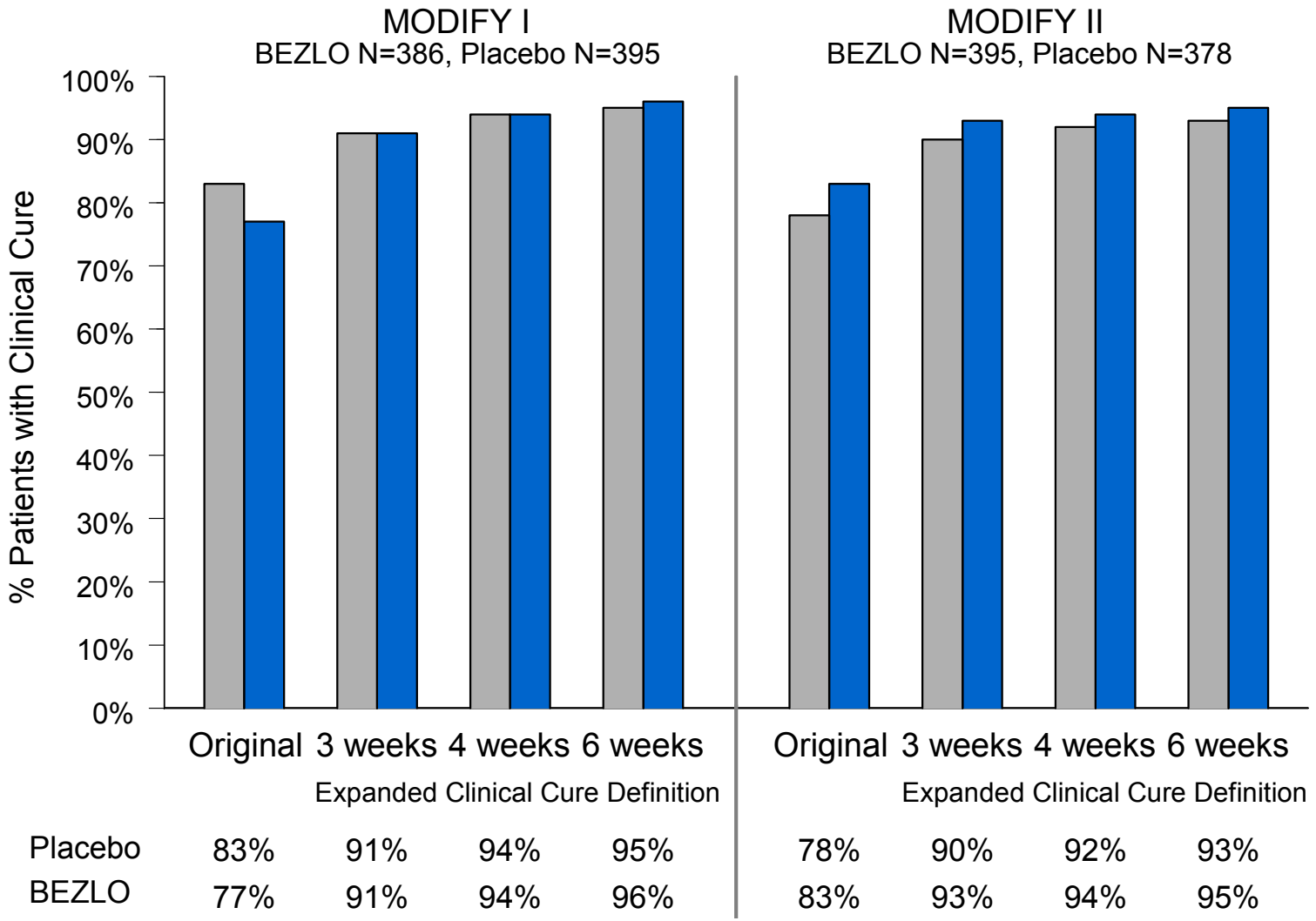
# Sensitivity Analyses: Time to Clinical Cure – Expanded Definition (MODIFY II)



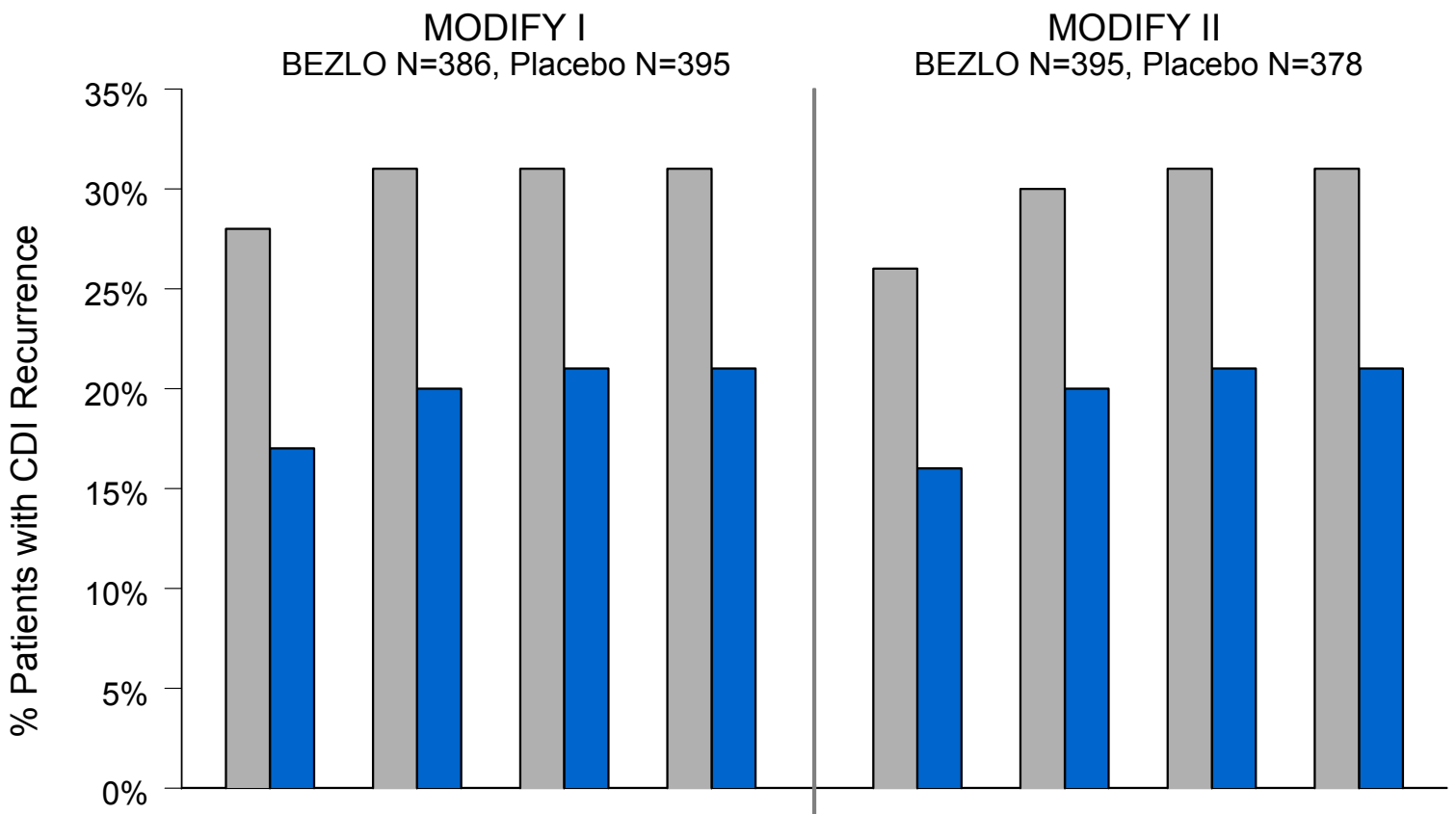

No. at Risk: KM Estimates (95% CI)

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 378 | 352: 9% ( 6, 12) | 106: 81% (77, 85) | 24: 93% (91, 96) | 12: 96% (94, 98) | 6: 98% (96, 99) |
| BEZLO | 395 | 363: 11% ( 8, 14) | 107: 80% (76, 84) | 15: 96% (94, 98) | 8: 98% (96, 99) | 6: 98% (97, 100) |

# BEZLO Does Not Impact Clinical Cure Rates

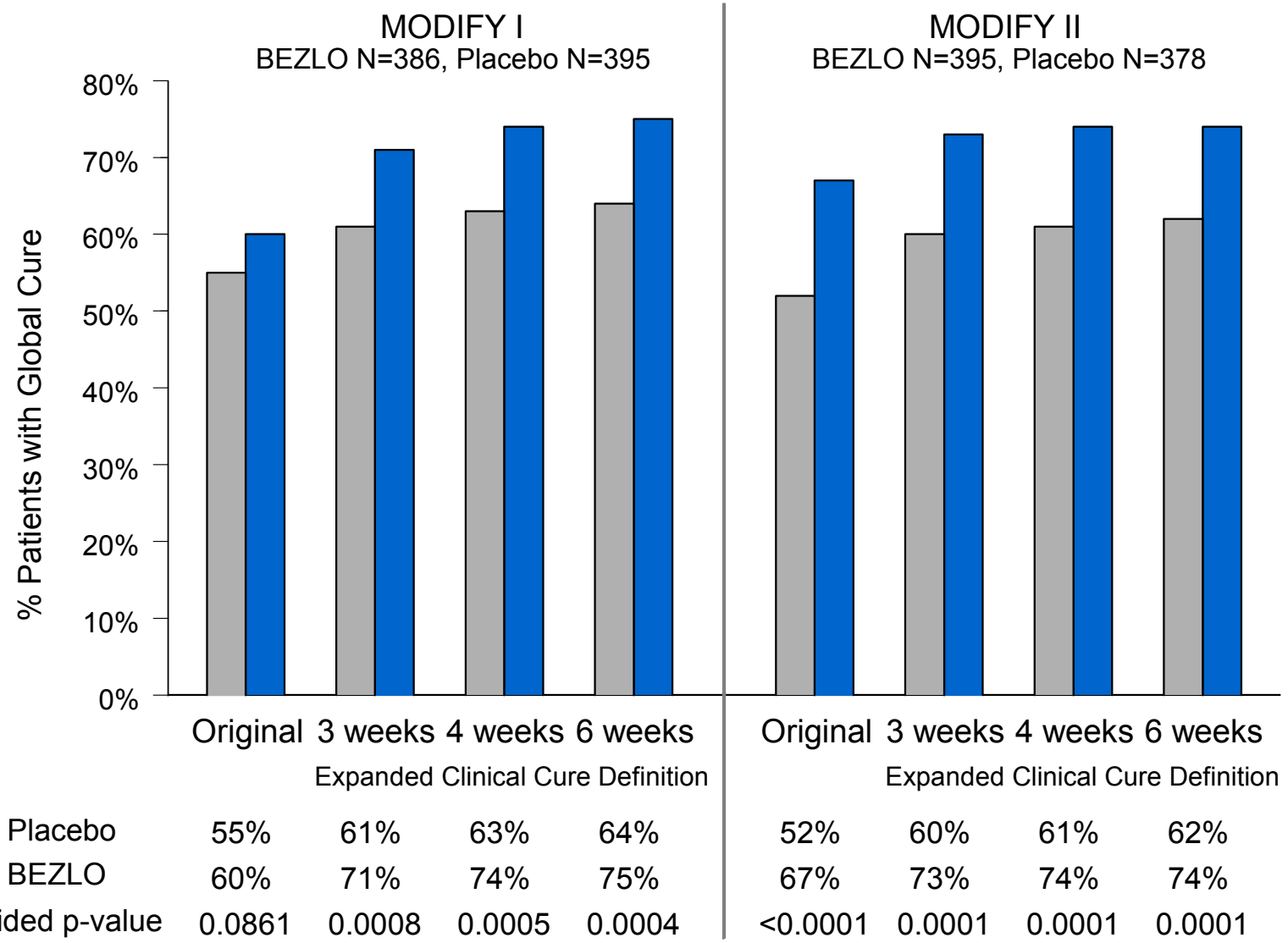


# BEZLO Reduces CDI Recurrence

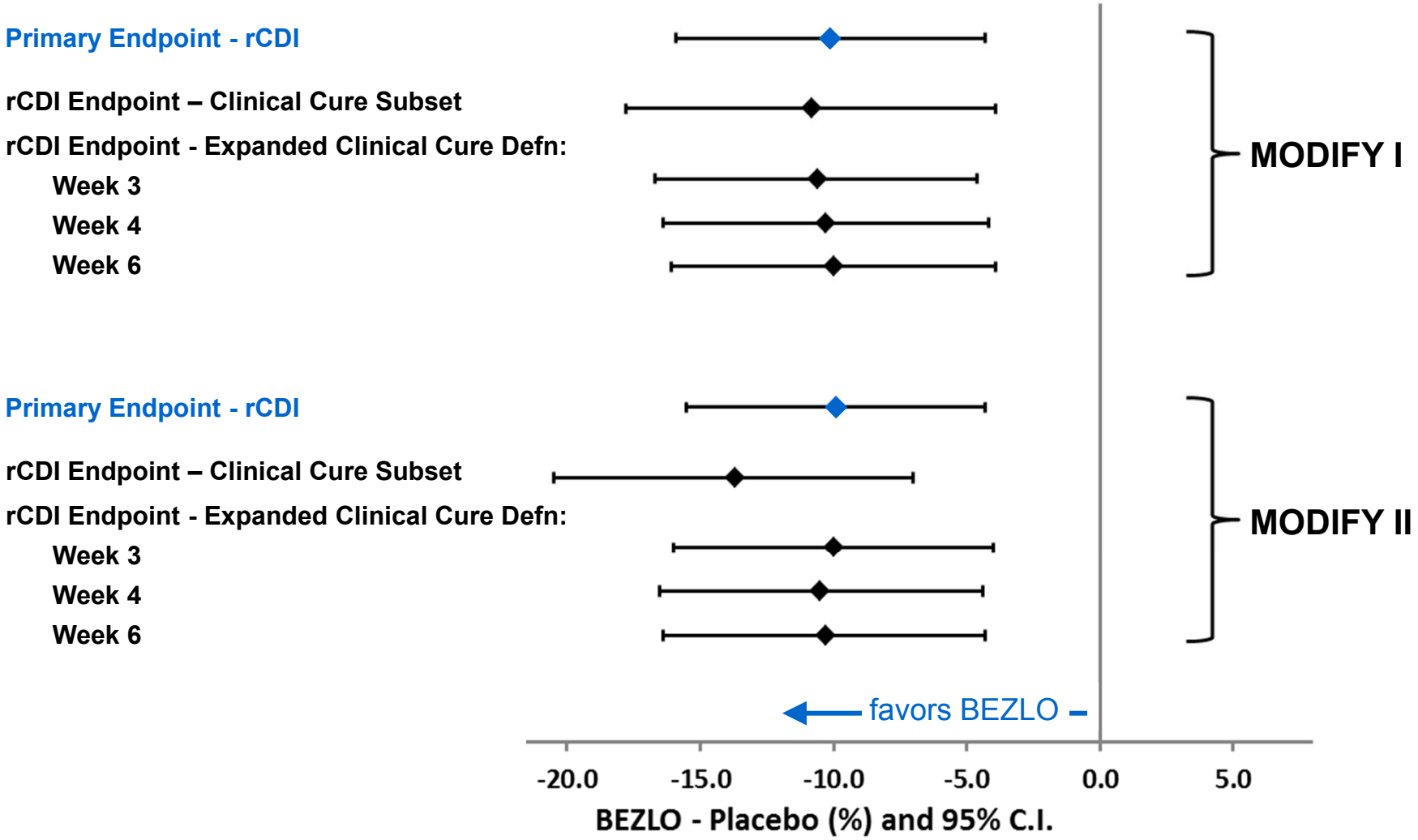



| | MODIFY I | | | | MODIFY II | | | |
|---|---|---|---|---|---|---|---|---|
| | Original | 3 weeks | 4 weeks | 6 weeks | Original | 3 weeks | 4 weeks | 6 weeks |
| Placebo | 28% | 31% | 31% | 31% | 26% | 30% | 31% | 31% |
| BEZLO | 17% | 20% | 21% | 21% | 16% | 20% | 21% | 21% |
| one-sided p-value | 0.0003 | 0.0003 | 0.0005 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 0.0005 |

# BEZLO Is Efficacious in Achieving Global Cure



# Robustness of Primary Efficacy Endpoint of CDI Recurrence




rCDI=CDI recurrence.

# Robustness of Primary Efficacy Endpoint Summary of Incomplete Data

| | Placebo N=773 n (%) | BEZLO N=781 n (%) |
|---|---|---|
| Incomplete Follow-up (Discontinuations) | 126 (16%) | 111 (14%) |
| Death | 56 | 52 |
| Withdrew consent | 39 | 34 |
| Lost to follow-up | 22 | 21 |
| Other | 9 | 4 |
| Incomplete assessment of diarrhea recurrence† | 26 (3%) | 43 (6%) |
| 1-2 days of diarrhea | 17 | 37 |
| >2 days of diarrhea | 9 | 6 |
| No CDI recurrence, but received CDI-active therapy during follow-up | 58 (8%) | 53 (7%) |

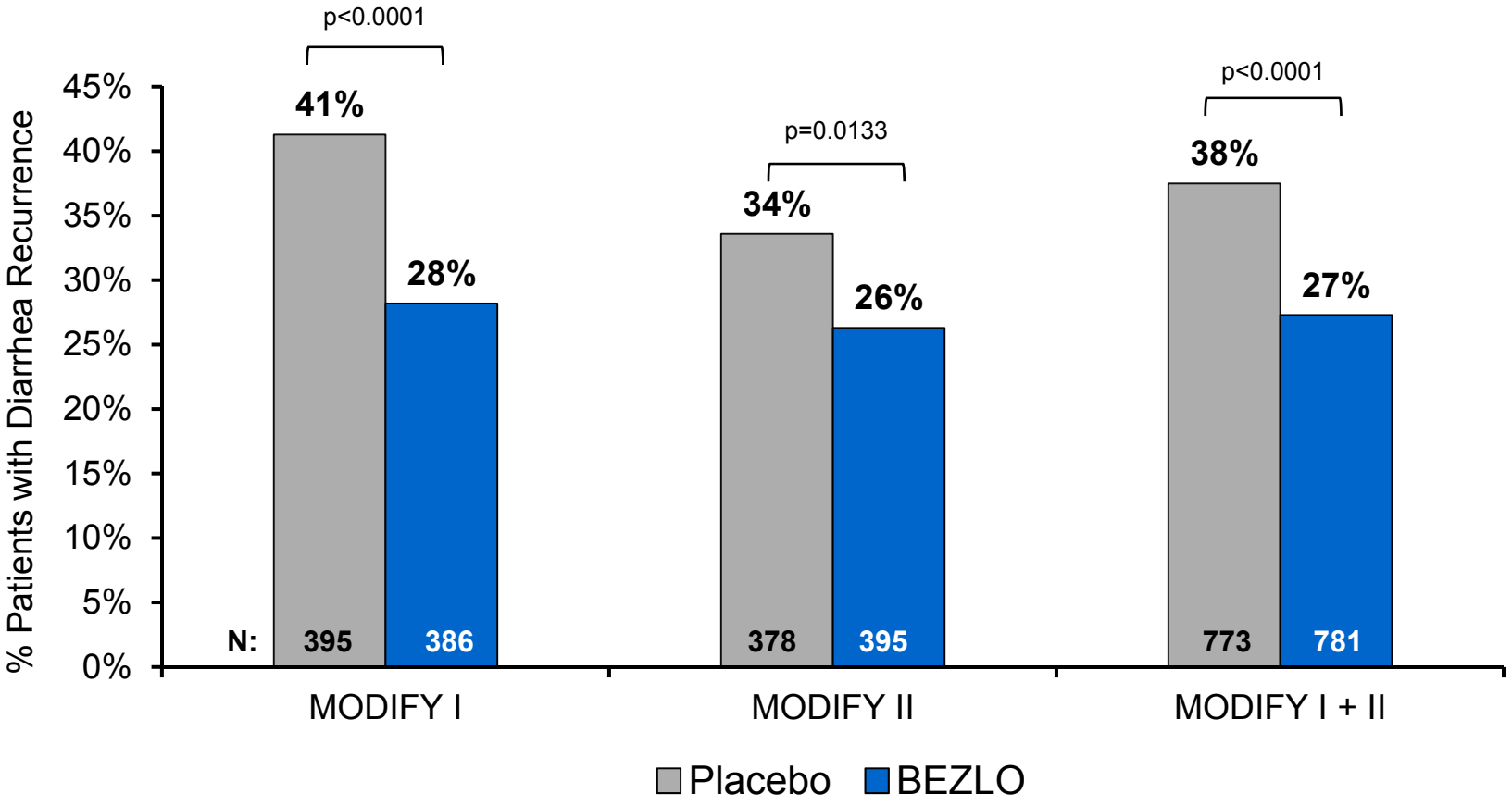
† Diarrhea recurrence after clinical cure of the baseline episode.

# Assessment of Robustness of Primary Efficacy Endpoint

- Sensitivity analyses assessing CDI recurrence in:
  - Clinical cure subset (secondary endpoint)
  - FAS using an expanded definition of clinical cure

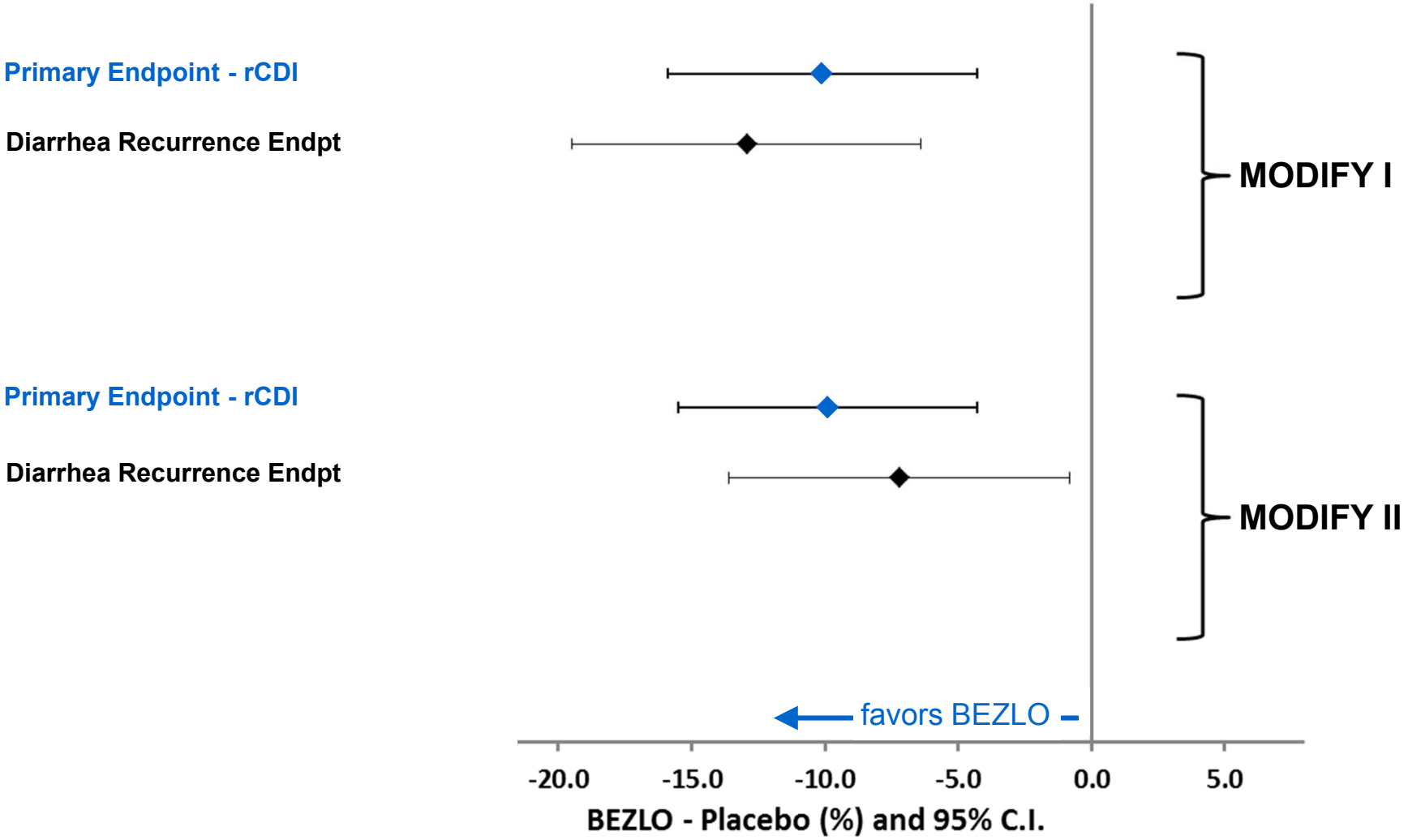
- Sensitivity analyses assessing impact of incomplete data
  - Diarrhea recurrence irrespective of etiology (exploratory endpoint)
  - CDI recurrence imputing patients meeting the following criteria as having a recurrence:
    - Discontinued from study
    - Discontinued from study and/or diarrhea with no toxigenic *C. difficile* test in the follow-up period
    - Discontinued from study and/or diarrhea with no toxigenic *C. difficile* test and/or CDI-active therapy in the follow-up period

# BEZLO Associated With Significantly Lower Diarrhea Recurrence Rate



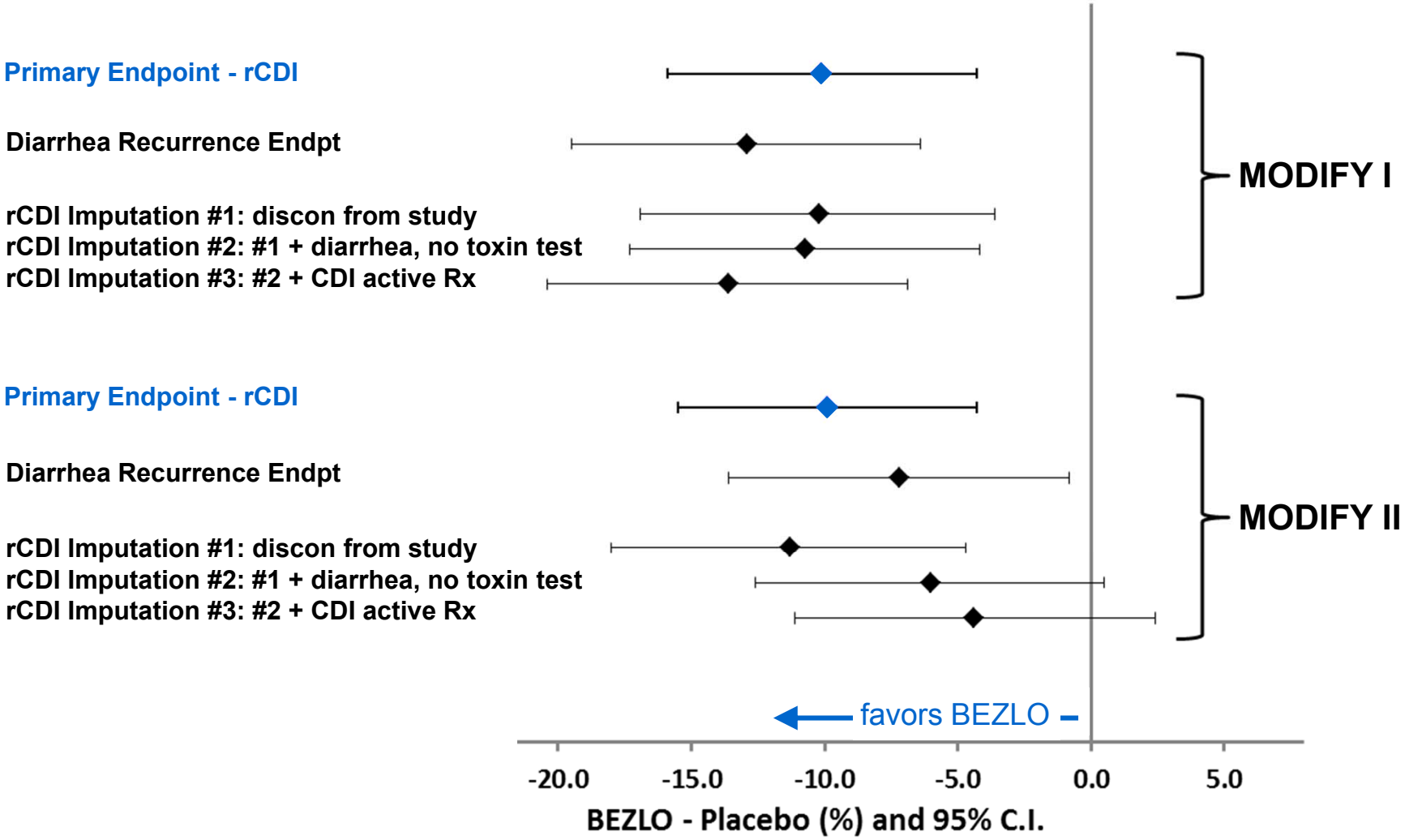

Note: p-values are one-sided.

# Robustness of Primary Efficacy Endpoint of CDI Recurrence



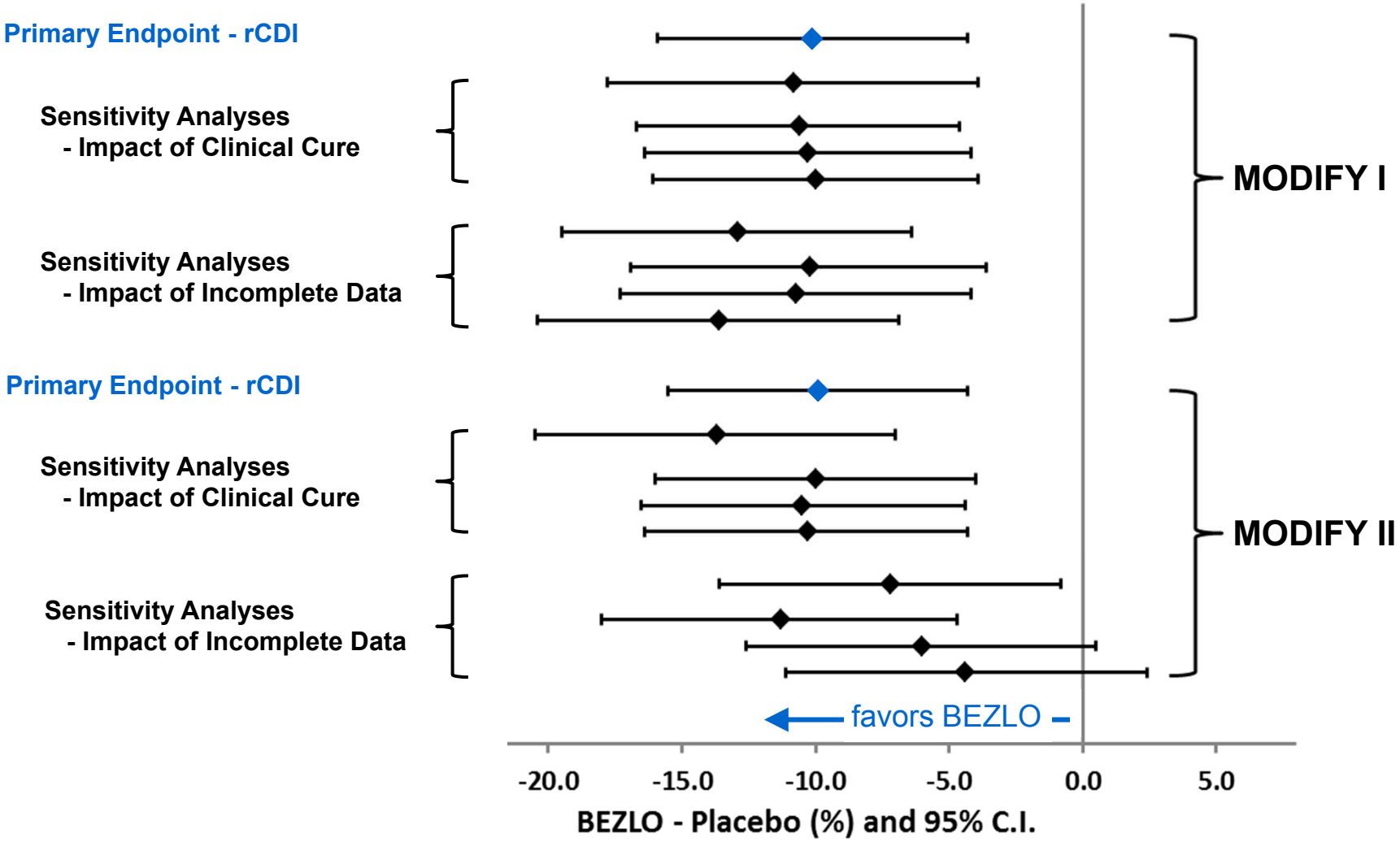

rCDI=CDI recurrence.

# Robustness of Primary Efficacy Endpoint of CDI Recurrence



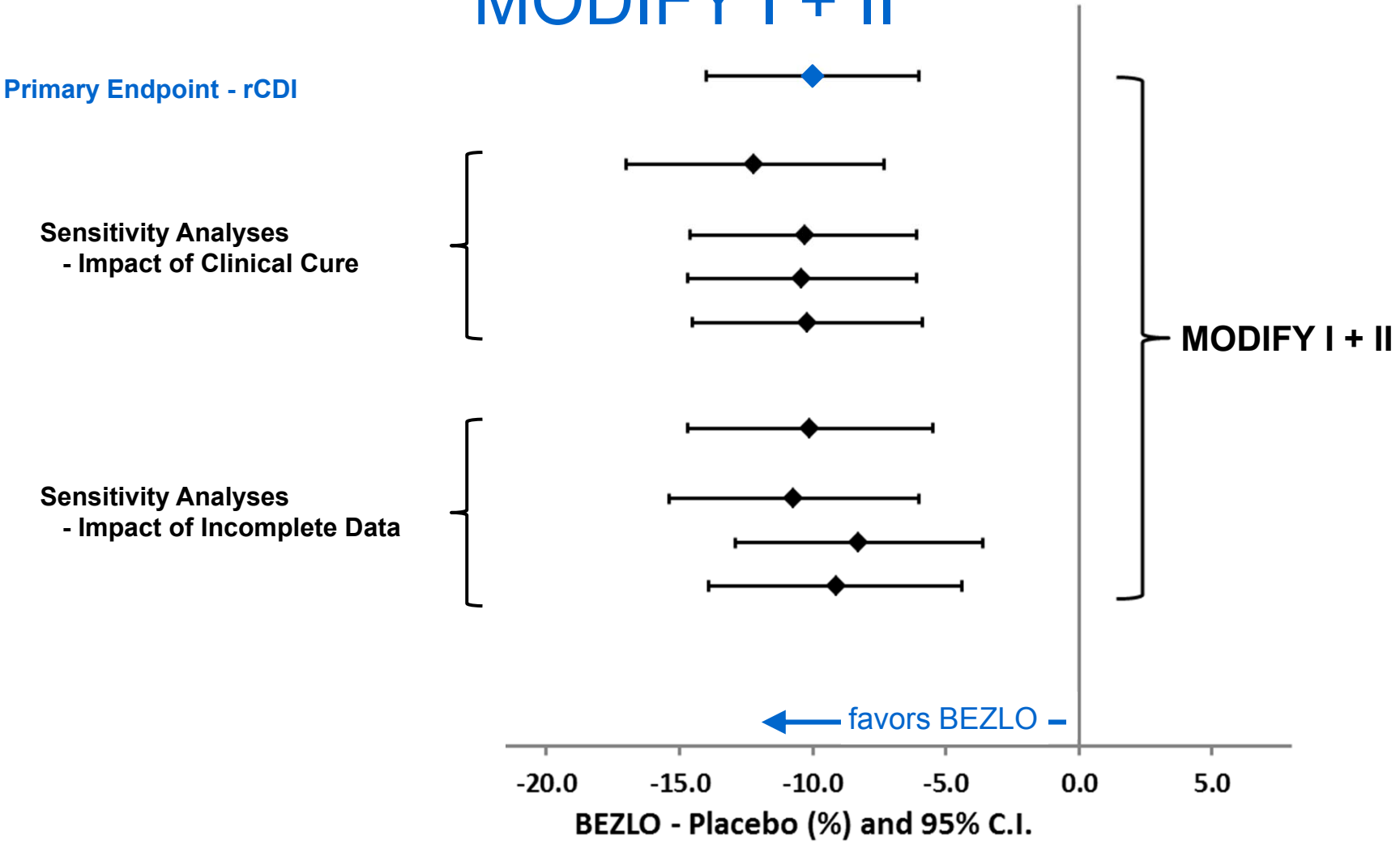

rCDI=CDI recurrence.

# Robustness of Primary Efficacy Endpoint of CDI Recurrence




rCDI=CDI recurrence.

# Summary of Sensitivity Analyses Assessing the Robustness of CDI Recurrence Endpoint MODIFY I + II




rCDI=CDI recurrence.

# Efficacy Conclusions

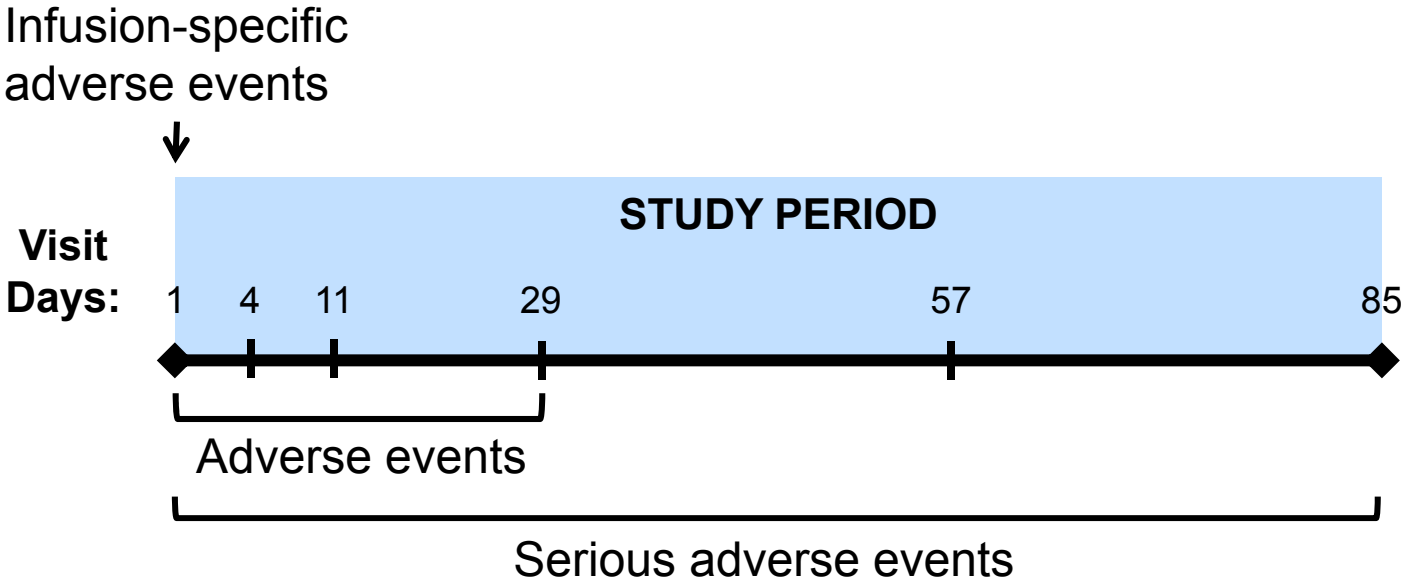
- A single dose of 10 mg/kg bezlotoxumab is superior to placebo in preventing CDI recurrence through 12 weeks follow-up period, in patients receiving SoC antibiotics for CDI
  - CDI recurrence rate is reduced by ~40%
  - Efficacy is consistent across MODIFY I and MODIFY II
  - Across important subpopulations, bezlotoxumab consistently reduces CDI recurrence rates compared to placebo
  - Sensitivity analyses consistently demonstrate that the primary endpoint of CDI recurrence and efficacy of bezlotoxumab in reducing CDI recurrence are robust
- Efficacy of the SoC antibiotic in achieving clinical cure is not diminished by bezlotoxumab

# Clinical Program: Safety

Yoshihiko Murata, MD, PhD

*Clinical Director, Bezlotoxumab Development*
*Infectious Disease Clinical Research*
*Merck Research Laboratories*

# Safety Assessments
## MODIFY I + II




| Monitoring Parameter(s) | Monitoring/Reporting Period |
|---|---|
| Adverse events (AEs) | Day 1 to Week 4 |
| Infusion-specific AEs | Day of infusion / day after infusion |
| Serious AEs | Day 1 to Week 12 |
| Safety laboratories | Day 1, Day 4, Day 11, Day 29 and unscheduled visits |
| Anti-drug antibody levels | Day 1 (pre-infusion), Day 29, Day 57, and Day 85 |

# Low Potential for Immunogenicity

- Bezlotoxumab has low potential to induce immunogenic responses in humans
- After administration of bezlotoxumab, no anti-drug antibodies (either binding or neutralizing) were detected in:
  - Phase 1 clinical trials involving healthy subjects (N=96)
    - After administration of two doses given three months apart (N=29)
  - Phase 2 clinical trials involving subjects with CDI (N=97)
  - Phase 3 clinical trials involving subjects with CDI (N=1414)

# Infusion-Specific Adverse Events

## MODIFY I + II, Integrated APaT Population

| Subjects in Population With: | Placebo N=781 n (%) | BEZLO N=786 n (%) | ACTO+BEZLO N=777 n (%) |
|---|---|---|---|
| Infusion-specific AEs | 59 (8) | 81 (10) | 62 (8) |
| Common infusion-specific AEs† | | | |
| Nausea | 13 (2) | 22 (3) | 10 (1) |
| Dizziness | 9 (1) | 10 (1) | 8 (1) |
| Headache | 8 (1) | 15 (2) | 15 (2) |
| Fatigue | 6 (1) | 9 (1) | 10 (1) |
| Pyrexia | 4 (1) | 8 (1) | 8 (1) |
| Infusion stopped due to AE | 0 | 1 (<1)‡ | 0 |

- The majority of infusion-specific AEs were mild (76%) or moderate (22%) in intensity
- No anaphylactic, anaphylactoid, or hypersensitivity reactions were observed

† Incidence ≥1% in at least one treatment group; by Preferred Term.
‡ Transient ventricular tachyarrhythmia which resolved.

# Adverse Event Summary During First 4 Weeks Following Infusion

## MODIFY I + II, Integrated APaT Population

| Subjects in Population: | Placebo N=781 n (%) | BEZLO N=786 n (%) | ACTO+BEZLO N=777 n (%) |
|---|---|---|---|
| With one or more AEs | 478 (61) | 485 (62) | 455 (59) |
| With drug-related AEs† | 46 (6) | 59 (8) | 50 (6) |
| With serious AEs | 167 (21) | 156 (20) | 123 (16) |
| With drug-related serious AEs† | 2 (<1) | 4 (1) | 5 (1) |
| Who died | 32 (4) | 32 (4) | 28 (4) |

† Causality as assessed by the investigator, who was blinded to the subject's treatment assignment.

# Most Common† Adverse Events Reported During First 4 Weeks Following Infusion

## MODIFY I + II, Integrated APaT Population

| Subjects in Population With: | Placebo N=781 n (%) | BEZLO N=786 n (%) | ACTO+BEZLO N=777 n (%) |
|---|---|---|---|
| *C. difficile* infection‡ | 48 (6) | 23 (3) | 27 (3) |
| Diarrhea | 45 (6) | 47 (6) | 46 (6) |
| Nausea | 39 (5) | 52 (7) | 47 (6) |
| Urinary tract infection | 35 (4) | 32 (4) | 24 (3) |
| Abdominal pain | 34 (4) | 34 (4) | 32 (4) |
| Pyrexia | 27 (3) | 36 (5) | 31 (4) |
| Headache | 24 (3) | 35 (4) | 33 (4) |

† Incidence ≥4% in at least one treatment group; by Preferred Term.
‡ *C. difficile* infection was to be reported as an AE only if it was serious.

# Serious Adverse Event Summary During 12 Weeks Following Infusion

## MODIFY I + II, Integrated APaT Population

| Subjects in Population: | Placebo N=781 n (%) | BEZLO N=786 n (%) | ACTO+BEZLO N=777 n (%) |
|---|---|---|---|
| With serious AEs | 255 (33) | 231 (29) | 212 (27) |
| Who died | 59 (8) | 56 (7) | 51 (7) |
| With drug-related serious AEs† | 2 (<1) | 4 (1) | 6 (1) |
| With drug-related serious AEs who died† | 0 | 1 (<1) | 2 (<1) |

† Causality as assessed by the investigator, who was blinded to the subject's treatment assignment.

# Most Common† Serious Adverse Events Reported During 12 Weeks Following Infusion

## MODIFY I + II, Integrated APaT Population

| Subjects in Population With: | Placebo N=781 n (%) | BEZLO N=786 n (%) | ACTO+BEZLO N=777 n (%) |
|---|---|---|---|
| *C. difficile* infection | 54 (7) | 24 (3) | 31 (4) |
| Sepsis‡ | 38 (5) | 25 (3) | 24 (3) |
| Pneumonia | 20 (3) | 12 (2) | 14 (2) |
| Diarrhea | 12 (2) | 16 (2) | 10 (1) |
| Acute kidney injury | 10 (1) | 6 (1) | 4 (1) |
| Urinary tract infection | 9 (1) | 15 (2) | 11 (1) |
| Cardiac failure§ | 7 (1) | 17 (2) | 17 (2) |

† Incidence ≥1% in at least one treatment group; by individual Preferred Term unless otherwise noted.
‡ Preferred Terms: bacteraemia, device related sepsis, fungaemia, sepsis, septic shock, urosepsis, and viraemia.
§ Preferred Terms: cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive.

# 41 Subjects With SAE of Cardiac Failure: Baseline Factors

| Baseline Factor | Placebo N=7 n (%) | BEZLO N=17 n (%) | ACTO+BEZLO N=17 n (%) |
|---|---|---|---|
| Age<br>Median, Years<br>≥75 Years | <br>82<br>6 (86) | <br>79<br>10 (59) | <br>81<br>14 (82) |
| Inpatient | 7 (100) | 16 (94) | 16 (94) |
| Charlson Comorbidity Index ≥3 | 5 (71) | 15 (88) | 15 (88) |
| Horn's Index Major/Extreme | 6 (86) | 10 (59) | 7 (41) |
| Severe CDI | 3 (43) | 8 (47) | 4 (24) |
| Medical History<br>Any cardiac condition<br>Cardiac failure/cardiomyopathy† | <br>6 (86)<br>5 (71) | <br>15 (88)<br>12 (71) | <br>15 (88)<br>12 (65) |

† Includes heart failure, heart failure acute, heart failure chronic, heart failure congestive, right ventricular failure, left ventricular dysfunction, and all cardiac terms containing myopathy.

# 41 Subjects With SAE of Cardiac Failure: Summary of Safety

| | Placebo N=7 n (%) | BEZLO N=17 n (%) | ACTO+BEZLO N=17 n (%) |
|---|---|---|---|
| Median timing of cardiac failure SAE, Days | 15 | 29 | 32 |
| Occurrence of cardiac failure SAE<br>on or before Day 28<br>after Day 28 | <br>5 (71)<br>2 (29) | <br>8 (47)<br>9 (53) | <br>8 (47)<br>9 (53) |
| Drug-related SAE of cardiac failure | 0 | 0 | 0 |
| Any death<br>on or before Day 28<br>between Day 29-56<br>between Day 57-84 | 4 (57)<br>2<br>2<br>0 | 7 (41)<br>2<br>3<br>2 | 7 (41)<br>5<br>0<br>2 |

- Events were often associated with concurrent conditions known to exacerbate CHF (e.g., new infection/worsening CDI)

# Preclinical Cardiac Safety Profile of Bezlotoxumab

- **BEZLO has a non-endogenous target (toxin B of *C. difficile*)**
- **No preclinical cardiac safety signal with BEZLO**
  - No tissue cross-reactivity seen in 38 mouse and human tissues tested *in vitro*, including cardiac tissues (heart and aorta)
  - No histological findings in cardiac tissues (including heart and aorta) or changes in hemodynamic parameters in the repeat-dose toxicity studies in mice

# CHF Subset: Baseline Factors
## MODIFY I + II, Integrated APaT Population

- Total of 325 (14%) subjects identified with baseline CHF as reported in Charlson Comorbidity Index

- As expected, this subset was an older, very ill patient population
  - Groups were not entirely balanced with regard to baseline CHF factors

| Baseline Factor | Placebo N=104 n (%) | BEZLO N=118 n (%) | ACTO+BEZLO N=103 n (%) |
|---|---|---|---|
| Age<br>Median, Years<br>≥75 Years | <br>77<br>62 (60) | <br>76<br>62 (53) | <br>79<br>67 (65) |
| Inpatient | 88 (85) | 102 (86) | 88 (85) |
| Charlson Comorbidity Index ≥5 | 39 (38) | 52 (44) | 46 (45) |
| Horn's Index Major/Extreme | 51 (49) | 58 (49) | 45 (44) |
| CHF Medications<br>Angiotensin-renin antagonists<br>Diuretics | <br>44 (42)<br>66 (63) | <br>40 (36)<br>80 (68) | <br>35 (34)<br>65 (63) |

# CHF Subset: Adverse Event Summary
## MODIFY I + II, Integrated APaT Population

| Week 4 | Placebo N=104 n (%) | BEZLO N=118 n (%) | ACTO+BEZLO N=103 n (%) |
|---|---|---|---|
| With ≥1 AE | 67 (64) | 85 (72) | 67 (65) |
| With ≥1 cardiac AE | 11 (11) | 13 (11) | 10 (10) |
| With ≥1 SAE | 35 (34) | 43 (36) | 27 (26) |
| With ≥1 cardiac SAE | 6 (6) | 11 (9) | 5 (5) |
| Any death | 7 (7) | 15 (13) | 13 (13) |
| Cardiac death | 4 (4) | 6 (5) | 4 (4) |

| Week 12 | Placebo N=104 n (%) | BEZLO N=118 n (%) | ACTO+BEZLO N=103 n (%) |
|---|---|---|---|
| With ≥1 SAE | 50 (48) | 63 (53) | 46 (45) |
| With ≥1 cardiac SAE | 9 (9) | 21 (18) | 15 (15) |
| Any death | 13 (13) | 23 (19) | 18 (17) |
| Cardiac death | 5 (5) | 9 (8) | 6 (6) |

# Safety Conclusions

- Bezlotoxumab, when given as a single IV 10 mg/kg dose in patients 18 years or older and receiving antibiotic therapy for CDI:
  - Is generally well tolerated
  - Has a safety profile which was similar to placebo
- Bezlotoxumab has a favorable safety/tolerability profile

# Bezlotoxumab
# Benefit/Risk Assessment

Professor Mark Wilcox, MD, FRCPath

*Professor of Medical Microbiology*
*Leeds Teaching Hospitals & University of Leeds*
*Lead on C. difficile, Public Health England*

# Continuing High Unmet **Patient** Need

- Patients suffer from debilitating, life-changing, painful diarrhea and other complications – poor options for recurrent CDI
- Out of every 10 patients with CDI, ~4 have an unsatisfactory outcome 
- Between 1 in 6 and 1 in 16 patients are dead at day 30[1,2]
- Only 2 (+1) approved therapeutic options for CDI
- No approved therapies for the prevention of CDI recurrence
- Antibiotic treatment for CDI does not prevent recurrence; it may extend the damage to the gut microbiota

[1] Lessa, et al. CID. 2012; [2] Planche, et al. Lancet ID. 2013.

# Continuing High Unmet **Medical** Need

- CDI is a global health problem with an increasing incidence in the US, Canada, and Europe[1,2]

- In the US in 2011[1]
  - estimated number of CDI cases was ~453,000
  - 29,000 associated deaths
  - 83,000 first recurrences
  - 53,000 additional recurrences[1,2]

[1] Lessa, et al. NEJM. 2015; [2] McFarland, et al. Am J Gastro. 2002.

# Continuing High Unmet **Medical** Need

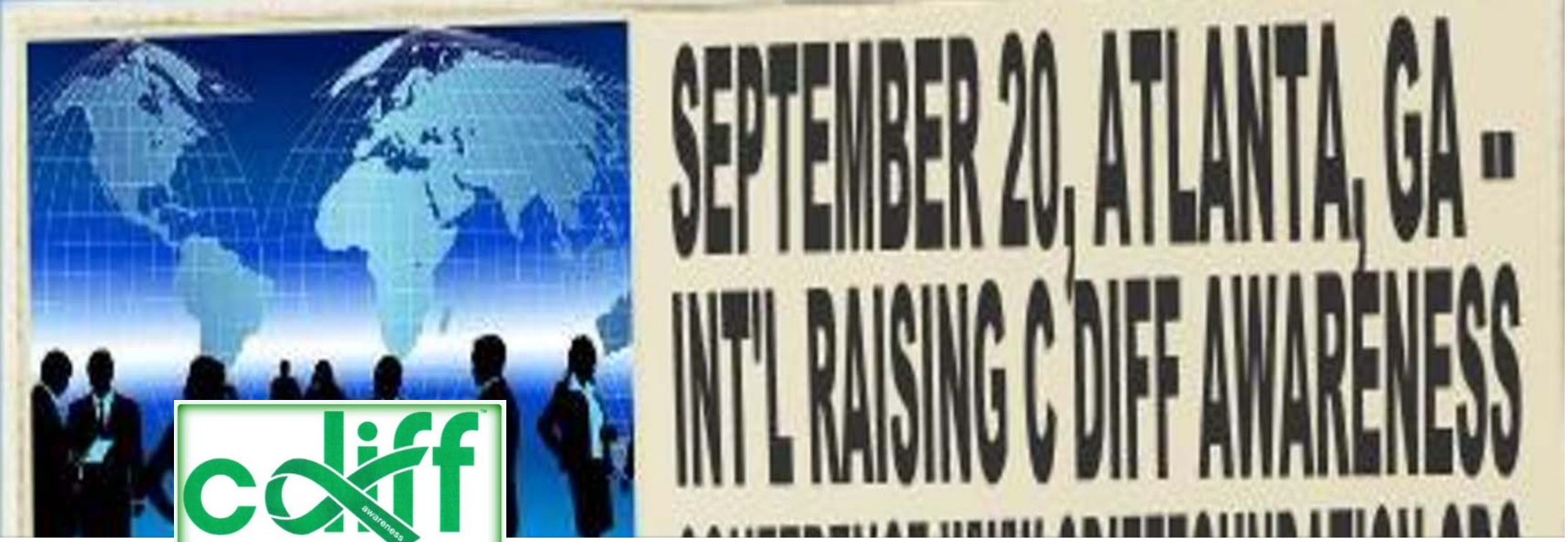
- Compared to primary CDI, recurrences are associated with
  - **33% higher** mortality rate by day 180[1]
  - **2.5 times higher** hospital re-admission rates[2]
  - **4 times higher** hospital re-admission days[2]

- High CDI attributable inpatient cost of recurrent CDI[3]

[1] Olsen, et al. CMI. 2015; [2] Olsen, et al. AJIC. 2015; [3] Dubberke, et al. ICHE. 2014.

# Continuing High Unmet **Societal** Need

- The families of patients have to cope with the illness, debility, isolation and loss due to CDI
- Few infectious diseases arouse so much concern, reflecting the protracted nature of recurrent CDI
- Patients and families often use words like "**battle**" and "**war**"
- Multiple *C. difficile* support groups exist
  - https://cdifffoundation.org
  - http://cdiffdiscuss.org
  - http://peggyfoundation.org




TWEETS 17K | FOLLOWING 3,059 | FOLLOWERS 3,046 | LIKES 11.5K

Follow

## C DIFF FOUNDATION

@cdiffFoundation

C Diff Foundation, educating and advocating for C difficile infection prevention,treatments, & environmental safety world-wide. cdifffoundation.org

Global

cdifffoundation.org

Joined September 2012

785 Photos and videos


**C DIFF FOUNDATION** @cdiffFoundation · Mar 23

September 20th #Cdiff2016 #Atlanta GA @DoubleTree #Cdiff International #RaisingCdiffAwareness Conference Health Expo


cdiffdiscuss.org
C. Difficile Support Group



# Case Histories and Updates

NEWTOPIC*

| ANNOUNCEMENTS | REPLIES | VIEWS |
|---|---|---|
| Case Histories<br>by » Wed Jan 21, 2015 1:04 am | 0 | 218 |
| RULES ON POSTING CASE HISTORIES<br>by » Sat Dec 10, 2005 9:14 pm | 0 | 2747 |

| TOPICS | REPLIES | VIEWS |
|---|---|---|
| At a loss of what to do<br>by » Mon Apr 25, 2016 8:26 pm | 2 | 176 |
| No Hospital Stay or Antibiotic Use<br>by » Sun Apr 24, 2016 7:59 pm | 0 | 64 |
| battle with the beast<br>by » Tue Sep 29, 2015 11:08 am | 7 | 1844 |
| Where I'm at in this battle<br>by » Fri Feb 26, 2016 4:31 pm | 0 | 638 |
| 26 year old, M, DIY FMT / Colon FMT, IBS-recoverying<br>by » Sun Feb 14, 2016 12:21 am | 0 | 250 |
| C-diff/gastritis/esophagitis<br>by » Tue Dec 01, 2015 8:23 am | 1 | 233 |
| My story with Cdiff<br>by » Tue Oct 27, 2015 4:51 am | 2 | 307 |
| Mary's First CDiff Battle<br>by » Tue Feb 12, 2008 9:39 pm | 13 | 2968 |
| My war with C-diff<br>by » Sat Jul 11, 2015 8:29 am | 0 | 399 |

# Bezlotoxumab Benefit/Risk Assessment

**A single IV dose of bezlotoxumab (10 mg/kg)**
**given to patients aged ≥18 years**
**while receiving antibiotic therapy for CDI:**

# Bezlotoxumab Benefit/Risk Assessment

**A single IV dose of bezlotoxumab (10 mg/kg) given to patients aged ≥18 years while receiving antibiotic therapy for CDI:**

- Generally well tolerated
- A safety profile that was similar to placebo

# Bezlotoxumab Benefit/Risk Assessment

**A single IV dose of bezlotoxumab (10 mg/kg) given to patients aged ≥18 years while receiving antibiotic therapy for CDI:**

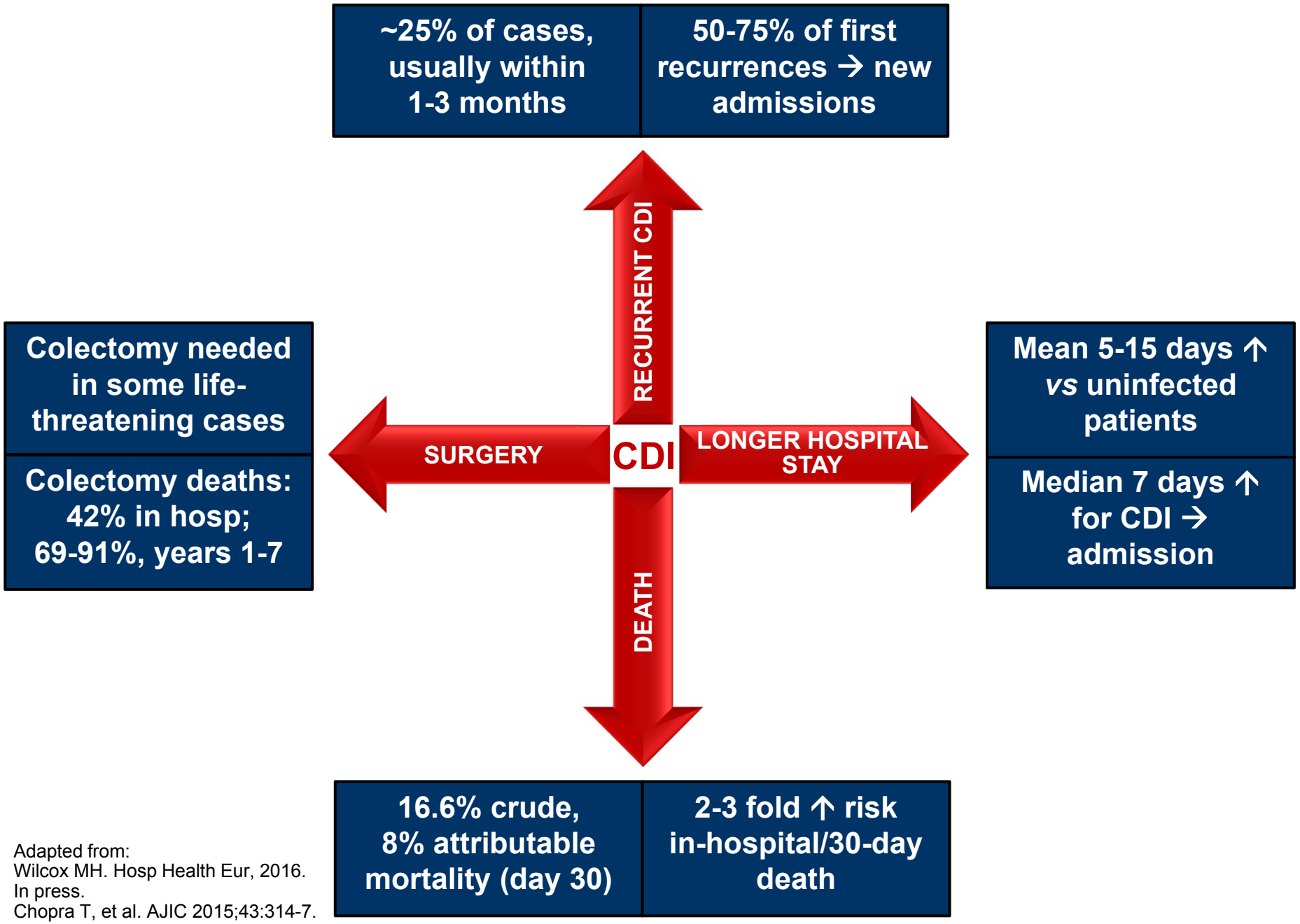
- Efficacy provided by bezlotoxumab is **prevention of CDI recurrence** over the 12-week, at-risk period
- Efficacy confirmed in multiple sensitivity analyses
- Efficacy demonstrated across predefined, clinically important subgroups at high risk for recurrence
- Generally well tolerated
- A safety profile that was similar to placebo

# Bezlotoxumab Benefit/Risk Assessment

**Bezlotoxumab reduces CDI recurrence rate by ~40%**

- Number needed to treat (NNT) to prevent 1 CDI recurrence is low at 10 (6 in high-risk groups)
- In US, potential to prevent up to 50,000 CDIs annually
- Reduced CDI-related re-admissions and all-cause cumulative hospital days†
- Fewer CDI cases for antibiotic treatment
  *(potential to prevent antibiotic resistance)*
- Potential benefit to other patients
  *(preventing recurrences & spread)*

† Post-hoc analysis, data not included in BLA.




Adapted from:
Wilcox MH. Hosp Health Eur, 2016. In press.
Chopra T, et al. AJIC 2015;43:314-7.

# Summary and Conclusion

**CDC Antibiotic Resistance Threat:**
***Clostridium difficile***


Image from CDC. http://www.cdc.gov/drugresistance/threat-report-2013/.

# Summary and Conclusion

- Bezlotoxumab helps to address unmet **patient, medical** and **societal** needs due to CDI


Image from CDC. http://www.cdc.gov/drugresistance/threat-report-2013/.

# Summary and Conclusion

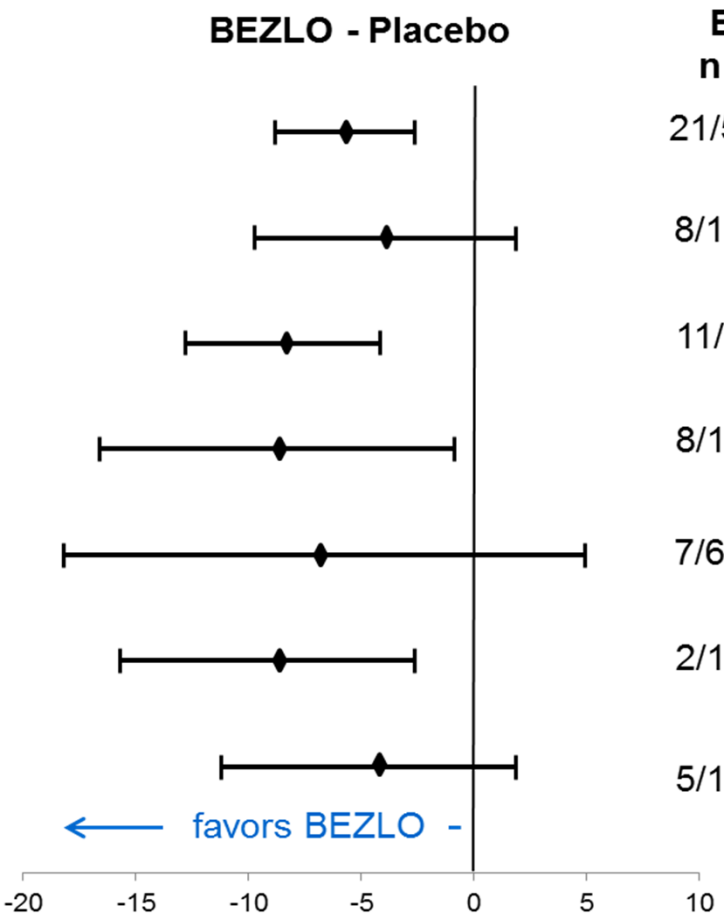
- Bezlotoxumab helps to address unmet **patient, medical** and **societal** needs due to CDI


- Bezlotoxumab has a positive benefit/risk profile for prevention of CDI recurrence

Image from CDC. http://www.cdc.gov/drugresistance/threat-report-2013/.

# Backup Slides Shown

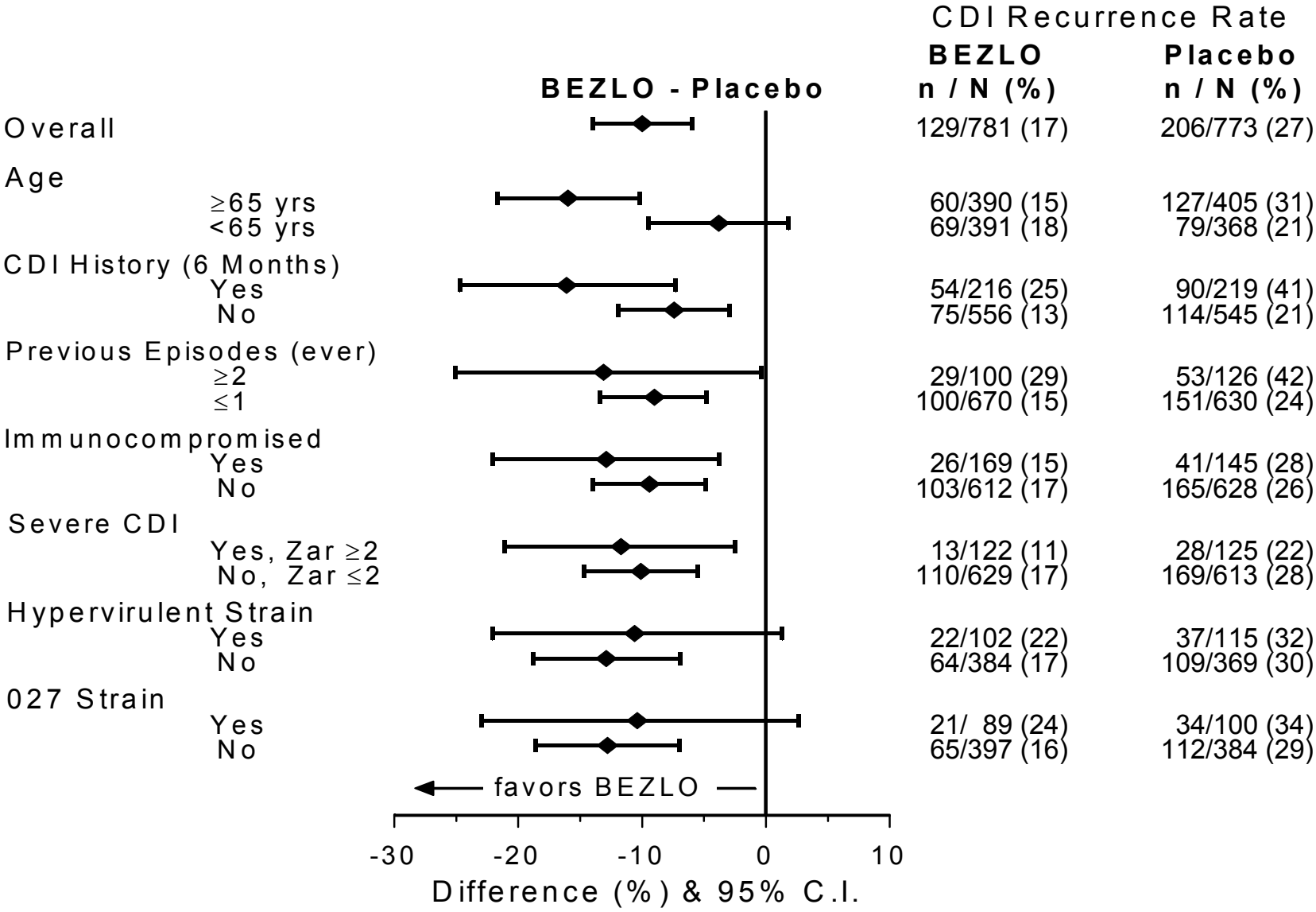
# Recurrent CDI Characteristics
# CDI-Associated 30-day Readmissions (MODIFY I+II)




| | BEZLO n / N (%) | Placebo n / N (%) | Absolute Difference |
|---|---|---|---|
| Overall | 21/530 (4.0) | 50/520 (9.6) | -5.7% |
| North America | 8/165 (4.8) | 14/162 (8.6) | -3.8% |
| Age ≥65 years | 11/298 (3.7) | 37/308 (12.0) | -8.3% |
| ≥1 CDI episodes in past 6 months | 8/127 (6.3) | 18/122 (14.8) | -8.5% |
| 027 strain* | 7/67 (10.4) | 14/81 (17.3) | -6.8% |
| Severe CDI† | 2/113 (1.8) | 12/116 (10.3) | -8.6% |
| Immunocompromised‡ | 5/131 (3.8) | 9/112 (8.0) | -4.2% |

*Denominator is number of subjects with the 027 strain isolated from a baseline stool sample.
†Zar score ≥2 based on the following: (1) age>60 years old (1 point); (2) body temperature >38.3°C (>100°F) (1 point); (3) albumin level <2.5 mg/dL (1 point); (4) peripheral white blood cell count >15,000 cells/mm3 within 48 hours (1 point); (5) endoscopic evidence of pseudomembranous colitis (2 points); and (6) treatment in an intensive care unit (2 points)
‡Defined on the basis of a subject's medical history or use of immunosuppressive therapy

# CDI Recurrence by With and Without Predefined Risk Factors (MODIFY I+II)



# Clinical Cure by Concomitant Systemic Antibiotic Use During SoC (MODIFY I+II)

| | | Clinical Cure Rates | |
|---|---|---|---|
| | Concomitant Antibiotic During SoC % (n/m) | With ABX During SoC % (n/m) | Without ABX During SoC % (n/m) |
| Placebo | 41.0 (317/773) | 74.1 (235/317) | 84.6 (386/456) |
| BEZLO | 37.4 (292/781) | 74.0 (216/292) | 83.6 (409/489) |

n = Number of subjects within subgroup that met the criteria for endpoint; m = Number of subjects within subgroup.
ABX=concomitant antibiotic
SoC=Standard of care

# CDI Recurrence by Concomitant Systemic Antibiotic Use After SoC (MODIFY I+II)

| | | CDI Recurrence Rates | |
|---|---|---|---|
| | Concomitant Antibiotic Following SoC % (n/m) | With ABX Following SoC % (n/m) | Without ABX Following SoC % (n/m) |
| Placebo | 35.6 (275/773) | 25.5 (70/275) | 27.3 (136/498) |
| BEZLO | 35.0 (273/781) | 16.5 (45/273) | 16.5 (84/508) |

n=Number of subjects within subgroup that met the criteria for endpoint.
m=Number of subjects within subgroup.
SoC = Standard of Care.
ABX=concomitant antibiotic

# Global Cure by Region (US/Ex-US) (MODIFY I+II)

| Enrollment in US vs. ex-US | Placebo N=773 | BEZLO N=781 |
|---|---|---|
| US | | |
| % (n/m) | 51.4 (163/317) | 59.9 (184/307) |
| Difference (95% CI†) vs. Placebo | | 8.5 (0.7, 16.2) |
| Ex-US | | |
| % (n/m) | 55.3 (252/456) | 65.8 (312/474) |
| Difference (95% CI†) vs. Placebo | | 10.6 (4.3, 16.8) |

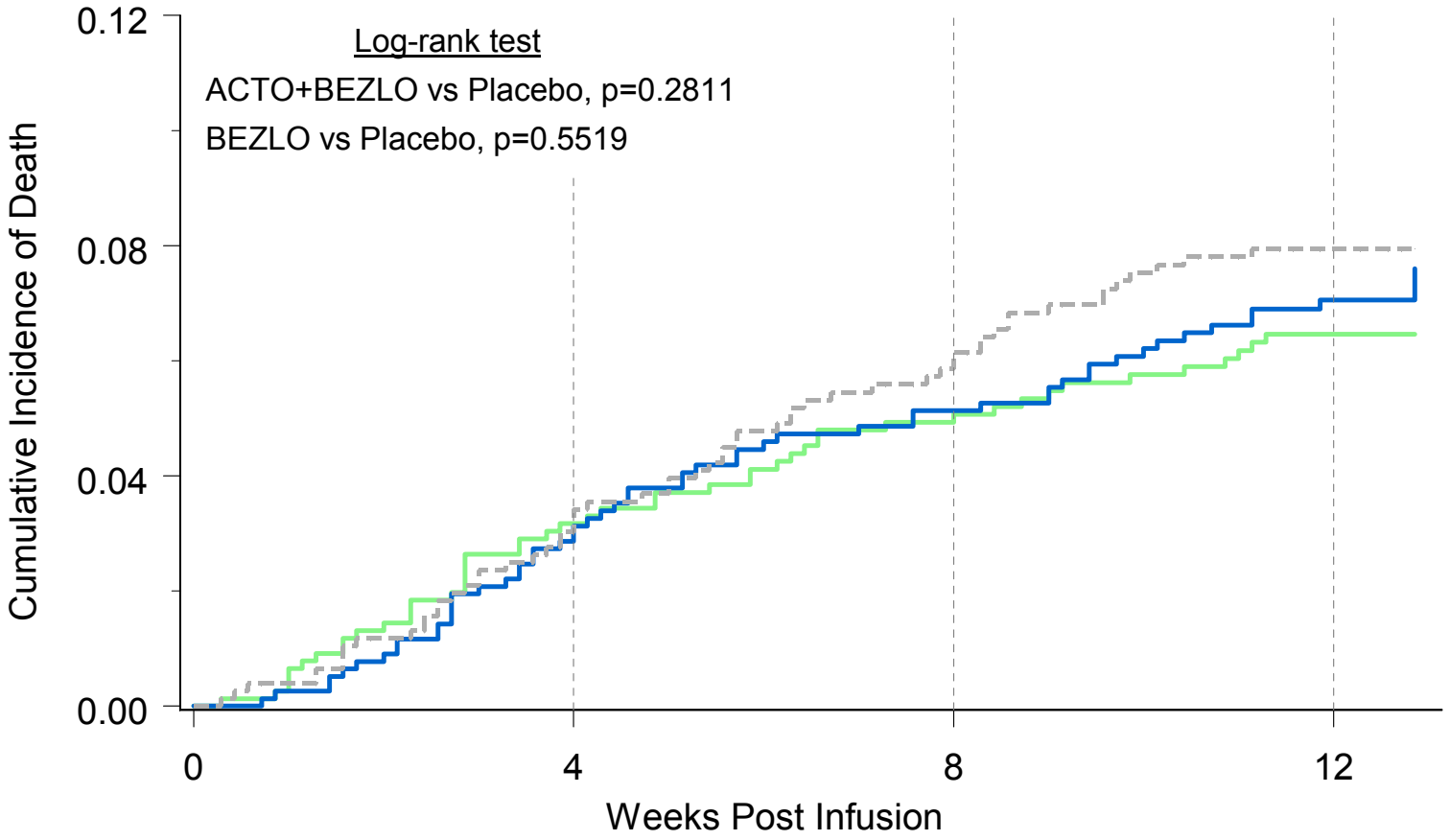
n = Number of subjects within subgroup that met the criteria for endpoint; m = Number of subjects within subgroup.
† Based on the Miettinen and Nurminen method without stratification.

# CDI Recurrence by Baseline Local Laboratory Test (MODIFY I+II)

| | Placebo<br>N=773<br>% (n/m) | BEZLO<br>N=781<br>% (n/m) |
|---|---|---|
| Local Lab Test Type | | |
| EIA | 27.3 (105/385) | 14.5 (54/372) |
| PCR | 26.1 (88/337) | 19.6 (70/357) |
| Cell Cytotoxicity Assay | 33.3 (2/6) | 10.0 (1/10) |
| Culture | 24.4 (11/45) | 9.5 (4/42) |

n=Number of subjects with designated local laboratory test used for baseline CDI diagnosis that met the criteria for endpoint.
m=Number of subjects with designated local laboratory test used for baseline CDI diagnosis.
EIA=enzyme immune assay; PCR=polymerase chain reaction assay; Culture=culture with toxin detection or with strain typing.

# Time to Death (MODIFY I+II)




No. at Risk: KM Estimates (95% CI)

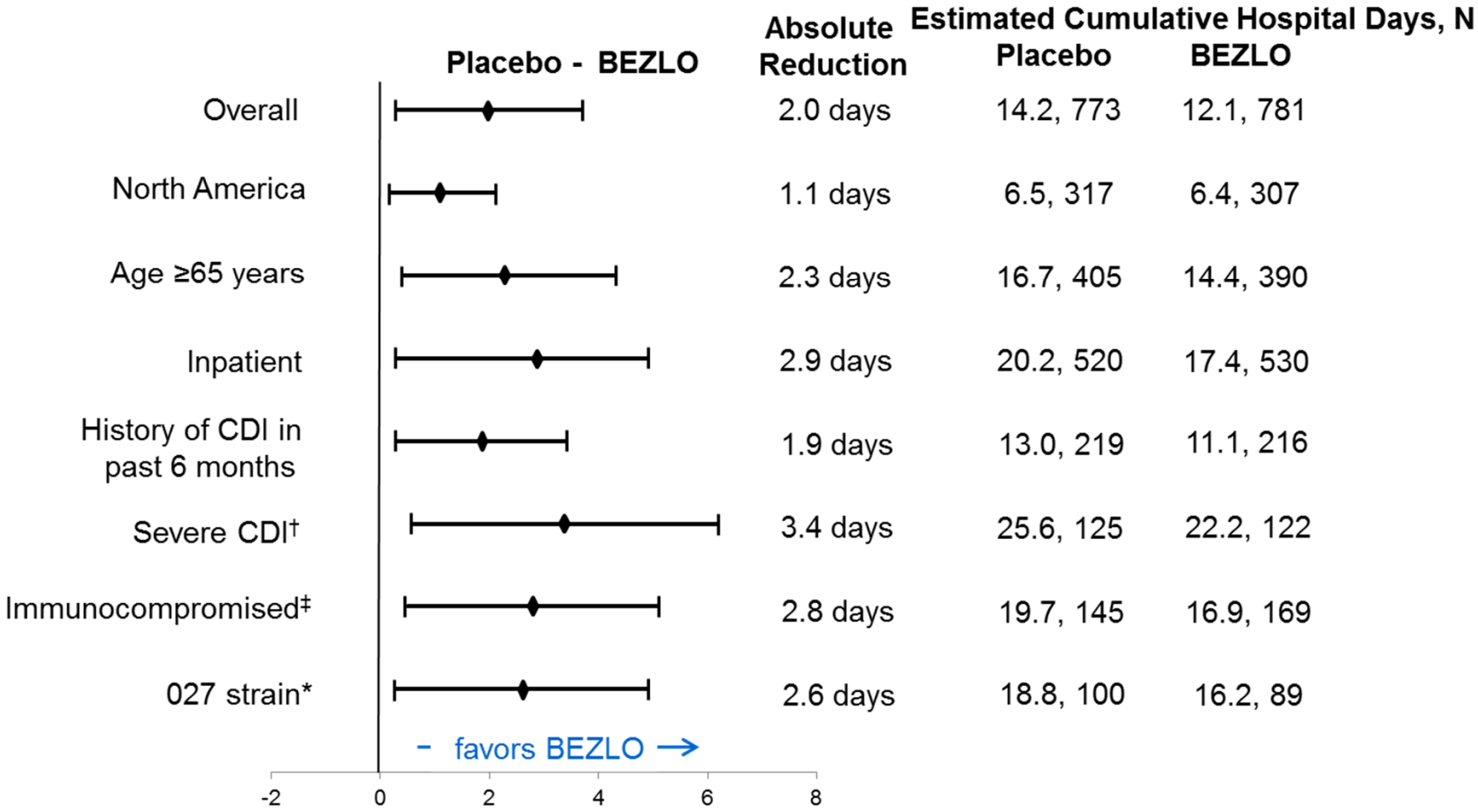
| | | | | |
|---|---|---|---|---|
| ACTO+BEZLO | 777 | 725: 3% (2, 4) | 694: 5% (3, 7) | 528: 6% (5, 8) |
| BEZLO | 786 | 739: 3% (2, 4) | 703: 5% (4, 7) | 539: 7% (5, 9) |
| Placebo | 781 | 729: 3% (2, 5) | 686: 6% (4, 8) | 525: 8% (6, 10) |

# Recurrent CDI Characteristics – Severity (MODIFY I+II)

| | Placebo N=206 | BEZLO N=129 |
|---|---|---|
| **Number of loose stools at onset of new episode** | | |
| Median | 4 | 4 |
| IQR | 3-6 | 3-5 |
| Min - Max | 3-20 | 3-22 |
| **Maximum number of loose stools during CDI episode** | | |
| Median | 6 | 4 |
| IQR | 4-8 | 3-6 |
| Min - Max | 3-23 | 3-22 |
| **Time to resolution of new episode (days), % (n/N)** | | |
| ≤2 | 47.6 (98/206) | 58.9 (76/129) |
| 3-4 | 28.6 (59/206) | 18.6 (24/129) |
| 5-7 | 16.0 (33/206) | 14.7 (19/129) |
| 8-10 | 3.9 (8/206) | 3.1 (4/129) |
| ≥10 | 3.9 (8/206) | 4.7 (6/129) |
| **Zar score ≥2, % (n/N)** | | |
| Yes | 9.7 (20/206) | 7.0 (9/129) |
| No | 77.7 (160/206) | 80.6 (104/129) |
| Unknown | 12.6 (26/206) | 12.4 (16/129) |

IQR=interquartile range. n=Number of subjects in the analysis population meeting the criteria.
N=Number of subjects included in the analysis population.

# Recurrent CDI Characteristics Estimated Cumulative Hospital Days Summed Over 84 Days (MODIFY I+II)




†Zar score ≥2 based on the following: (1) age>60 years old (1 point); (2) body temperature >38.3°C (>100°F) (1 point); (3) albumin level <2.5 mg/dL (1 point); (4) peripheral white blood cell count >15,000 cells/mm3 within 48 hours (1 point); (5) endoscopic evidence of pseudomembranous colitis (2 points); and (6) treatment in an intensive care unit (2 points)
‡Defined on the basis of a subject's medical history or use of immunosuppressive therapy

# Summary of AEs (MODIFY I - Interim Analysis)

| | Placebo N=166 n (%) | BEZLO N=165 n (%) | ACTO+ BEZLO N=165 n (%) | ACTO N=165 n (%) |
|---|---|---|---|---|
| Any AE to Week 4 post-infusion | 121 (73) | 120 (73) | 118 (72) | 128 (78) |
| Any drug-related AE | 10 (6) | 12 (7) | 12 (7) | 9 (5) |
| Treatment discontinued due to AE | 0 (0) | 1 (1) | 0 (0) | 0 (0) |
| Any serious AE to Week 12 post infusion | 54 (33) | 53 (32) | 41 (25) | 70 (42) |
| Any drug-related serious AE | 0 (0) | 3 (2) | 1 (1) | 1 (1) |
| AEs with fatal outcome | 10 (6) | 15 (9) | 8 (5) | 25 (15) |
| Infusion-specific AE† | 29 (17) | 26 (16) | 24 (15) | 24 (15) |
| Infusion-specific drug-related AE† | 8 (5) | 5 (3) | 6 (4) | 8 (5) |

Denominators and column header counts are the number of subjects in the APaT population.
Subjects are counted once per row, regardless of the number of events they may have.
† Infusion-specific AEs are events that occur within 24 hours of infusion that are identified by blinded medical review at Merck.

# AEs with Fatal Outcome (MODIFY I - ACTO Group )

| Subjects in Population With One or More Fatal Adverse Events (N=27) | n (%) |
|---|---|
| Cardiac arrest | 1 (<1) |
| Cardiac failure | 1 (<1) |
| Diarrhoea | 1 (<1) |
| Pancreatitis | 1 (<1) |
| Death | 1 (<1) |
| Multi-organ failure | 1 (<1) |
| Sudden cardiac death | 1 (<1) |
| Systemic inflammatory response syndrome | 1 (<1) |
| Graft versus host disease | 1 (<1) |
| *Clostridium difficile* sepsis | 1 (<1) |
| Pneumonia | 1 (<1) |

| Subjects in Population With One or More Fatal Adverse Events (N=27) | n (%) |
|---|---|
| Sepsis | 7 (3) |
| Septic shock | 3 (1) |
| Urinary tract infection | 1 (<1) |
| Failure to thrive | 1 (<1) |
| Burkitt's lymphoma | 1 (<1) |
| Gastric cancer | 1 (<1) |
| Lung neoplasm malignant | 1 (<1) |
| Pancreatic carcinoma | 1 (<1) |
| Cerebrovascular accident | 1 (<1) |
| Renal failure acute | 1 (<1) |
| Pneumonia aspiration | 1 (<1) |
| Respiratory failure | 2 (1) |

# AEs with Fatal Outcomes: Sepsis or Septic Shock (MODIFY I - ACTO Group)

| Demographics | Underlying Medical Conditions and Relevant Microbiological Data | Relative Day of Onset | Preferred Term | Duration | Intensity | Related |
|---|---|---|---|---|---|---|
| M/W/85Y | Recurrent UTI | 56 | Sepsis | 1 Wk | Severe | N |
| M/W/63Y | Gram-negative bacteremia, metastatic small cell Ca | 6 | Sepsis | 3 Days | Severe | N |
| F/W/72Y | Recurrent severe CDI with total colectomy | 24<br>25<br>25 | *C.Difficile* Sepsis<br>Sepsis<br>SIRS | 2.57 Wks<br>2.43 Wks<br>2.43 Wks | Severe<br>Severe<br>Severe | N<br>N<br>N |
| M/W/86Y | Pneumonia,<br>*P. aeruginosa* in urine | 13<br>19 | Sepsis<br>Respiratory Failure | 1 Wk<br>23 hrs | Severe<br>Severe | N<br>N |
| F/W/71Y | Hepatitis C, hepatocellular carcinoma, *S. pneumoniae* bacteremia | 71 | Septic Shock | 3 Days | Severe | N |
| F/W/80Y | Rheumatoid arthritis, *C. freundii* bacteremia | 21 | Sepsis | 4 Wks | Severe | N |
| M/W/88Y | Pneumonia, *S. aureus* bacteremia | 29 | Sepsis | 6 Days | Severe | N |
| M/W/75Y | Diabetes mellitus, L leg ulcers | 55 | Septic Shock | 5 Days | Severe | N |
| F/W/92Y | *K. pneumoniae* UTI | 19<br>23 | UTI<br>Sepsis | 6 Days<br>2 Days | Severe<br>Severe | N<br>N |
| M/W/77Y | Pneumonia, *K. pneumoniae/P. aeruginosa* in sputum | 75 | Septic Shock | 1.14 Wks | Severe | N |

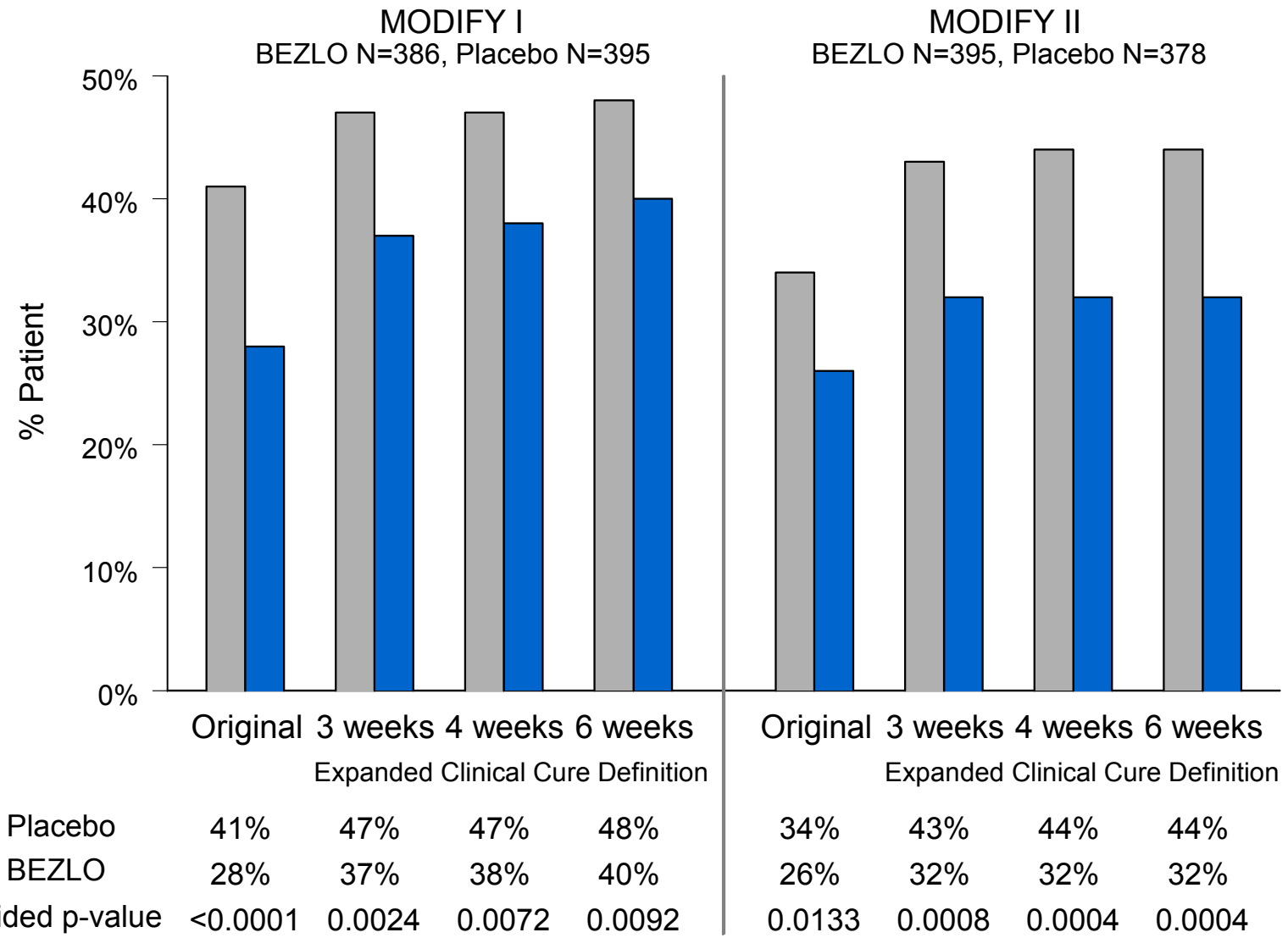
# Receipt of Fecal Microbiota Transplant (FMT) in Patients with CDI Recurrence, MODIFY I+II

| | Placebo N=206 n/N (%) | BEZLO N=129 n/N (%) | ACTO+BEZLO N=119 n/N (%) |
|---|---|---|---|
| Subjects Receiving FMT | 22 (11) | 4 (3) | 4 (3) |

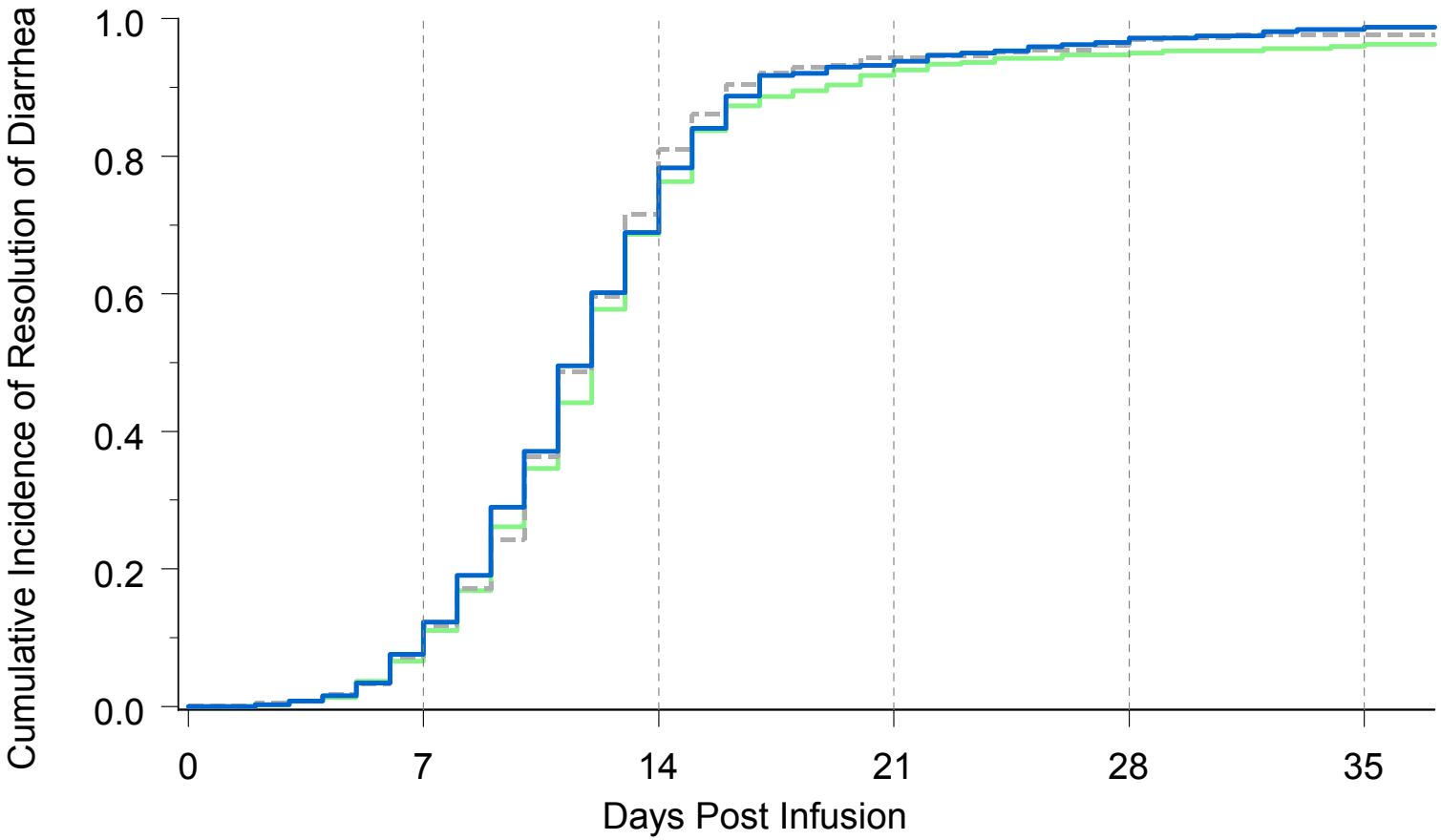
# Clinical Cure Rates using Expanded Definition of Clinical Cure

| Clinical Cure Definition | MODIFY I | | | | MODIFY II | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=395) | | BEZLO (N=386) | | Placebo (N=378) | | BEZLO (N=395) | |
| | n | % | n | % | n | % | n | % |
| **Original Definition** | **327** | **82.8%** | **299** | **77.5%** | **294** | **77.8%** | **326** | **82.5%** |
| **Expanded Definition** | | | | | | | | |
| 2 weeks | 313 | 79.2% | 297 | 76.9% | 296 | 78.3% | 308 | 78.0% |
| 3 weeks | 361 | 91.4% | 353 | 91.5% | 340 | 89.9% | 367 | 92.9% |
| 4 weeks | 370 | 93.7% | 364 | 94.3% | 349 | 92.3% | 372 | 94.2% |
| 6 weeks | 375 | 94.9% | 370 | 95.9% | 353 | 93.4% | 376 | 95.2% |
| 8 weeks | 377 | 95.4% | 371 | 96.1% | 354 | 93.7% | 377 | 95.4% |
| 12 weeks | 379 | 95.9% | 373 | 96.6% | 356 | 94.2% | 377 | 95.4% |

# Diarrhea Recurrence using Expanded Definition of Clinical Cure



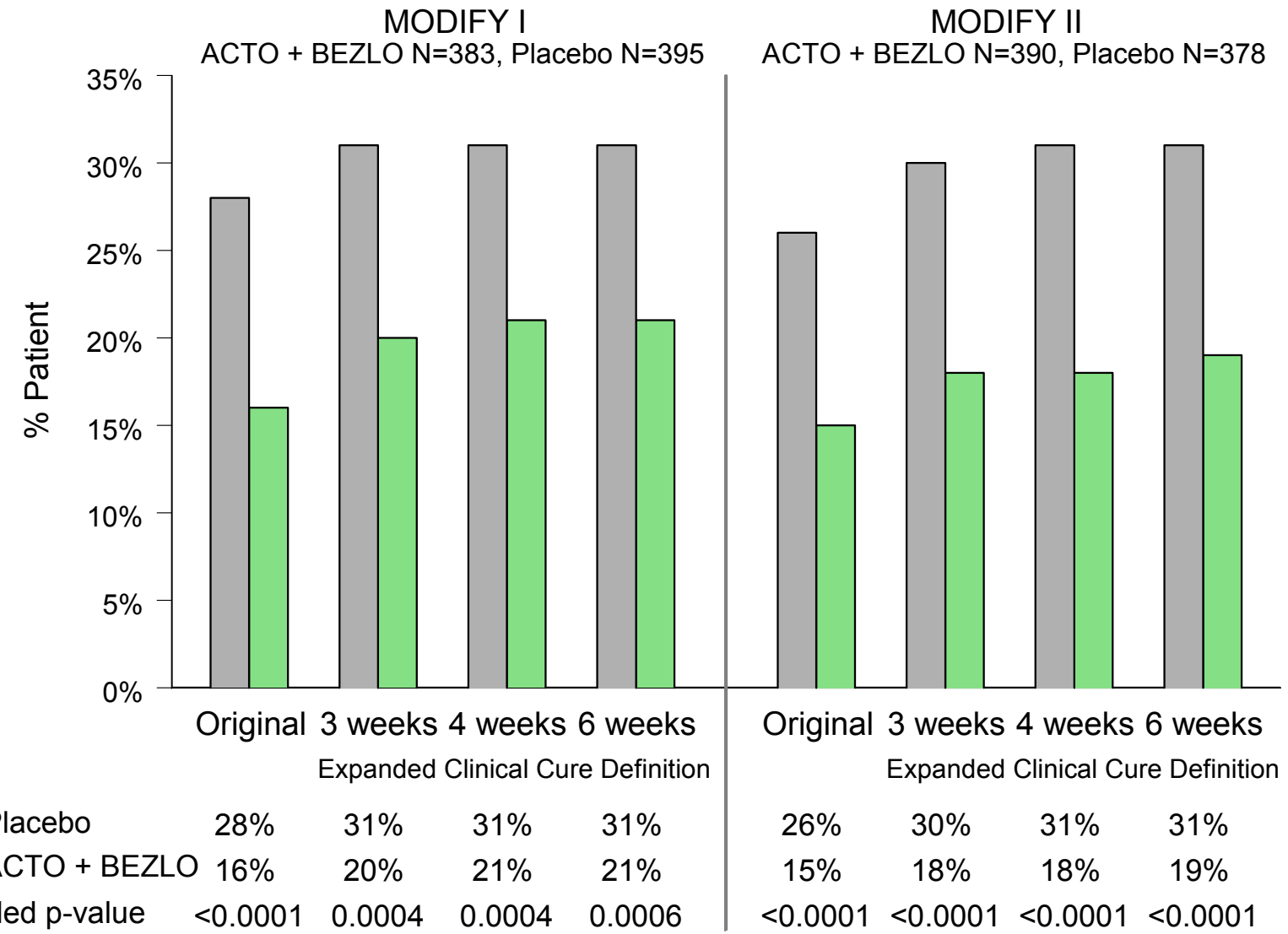
# Time to Clinical Cure – Expanded Definition (MODIFY I)



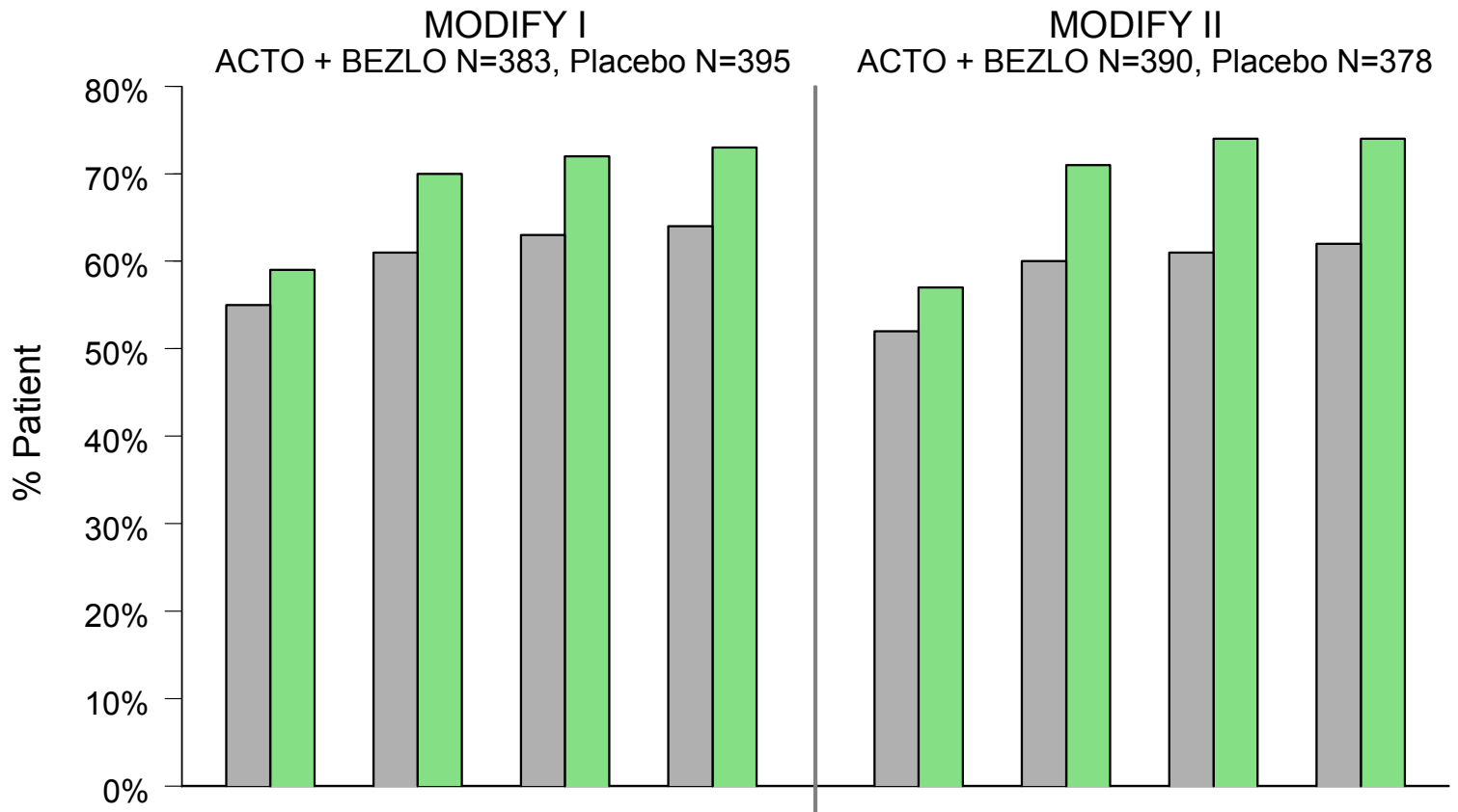

No. at Risk: KM Estimates (95% CI)

| | | | | | | |
|---|---|---|---|---|---|---|
| ACTO+BEZLO | 383 | 355: 11% (8, 14) | 115: 76% (72, 81) | 30: 93% (90, 95) | 19: 95% (93, 97) | 12: 96% (94, 98) |
| BEZLO | 386 | 354: 12% (9, 16) | 116: 78% (74, 82) | 23: 94% (91, 96) | 11: 97% (95, 99) | 5: 99% (98, 100) |
| Placebo | 395 | 364: 12% (9, 15) | 106: 81% (77, 85) | 20: 94% (92, 97) | 13: 97% (95, 99) | 8: 98% (96, 99) |

# CDI Recurrence using Expanded Definition of Clinical Cure



# Global Cure using Expanded Definition of Clinical Cure




| | MODIFY I | | | | MODIFY II | | | |
|---|---|---|---|---|---|---|---|---|
| | Original | 3 weeks | 4 weeks | 6 weeks | Original | 3 weeks | 4 weeks | 6 weeks |
| Placebo | 55% | 61% | 63% | 64% | 52% | 60% | 61% | 62% |
| ACTO + BEZLO | 59% | 70% | 72% | 73% | 57% | 71% | 74% | 74% |
| one-sided p-value | 0.1646 | 0.0038 | 0.0031 | 0.0028 | 0.0722 | 0.0005 | 0.0001 | 0.0001 |

# CDI Recurrence by CDI History (3 Months) (MODIFY I+II)

| | Placebo N=773 | BEZLO N=781 |
|---|---|---|
| **History of CDI (3 Months)** | | |
| Yes | | |
| % (n/m) | 41.6 (79/190) | 24.3 (45/185) |
| Difference (95% CI†) vs. Placebo | | -17.3 (-26.5, -7.8) |
| No | | |
| % (n/m) | 21.8 (125/574) | 14.3 (84/586) |
| Difference (95% CI†) vs. Placebo | | -7.4 (-11.9, -3.0) |
| Unknown | | |
| % (n/m) | 22.2 (2/9) | 0.0 (0/10) |
| **Number of Episodes in the Past (3 Months)** | | |
| 0 | | |
| % (n/m) | 21.8 (125/574) | 14.3 (84/586) |
| Difference (95% CI†) vs. Placebo | | -7.4 (-11.9, -3.0) |
| 1 | | |
| % (n/m) | 36.4 (48/132) | 20.0 (28/140) |
| Difference (95% CI†) vs. Placebo | | -16.4 (-26.8, -5.7) |
| ≥ 2 | | |
| % (n/m) | 52.6 (30/57) | 37.8 (17/45) |
| Difference (95% CI†) vs. Placebo | | -14.9 (-33.2, 4.7) |
| Unknown | | |
| % (n/m) | 30.0 (3/10) | 0.0 (0/10) |

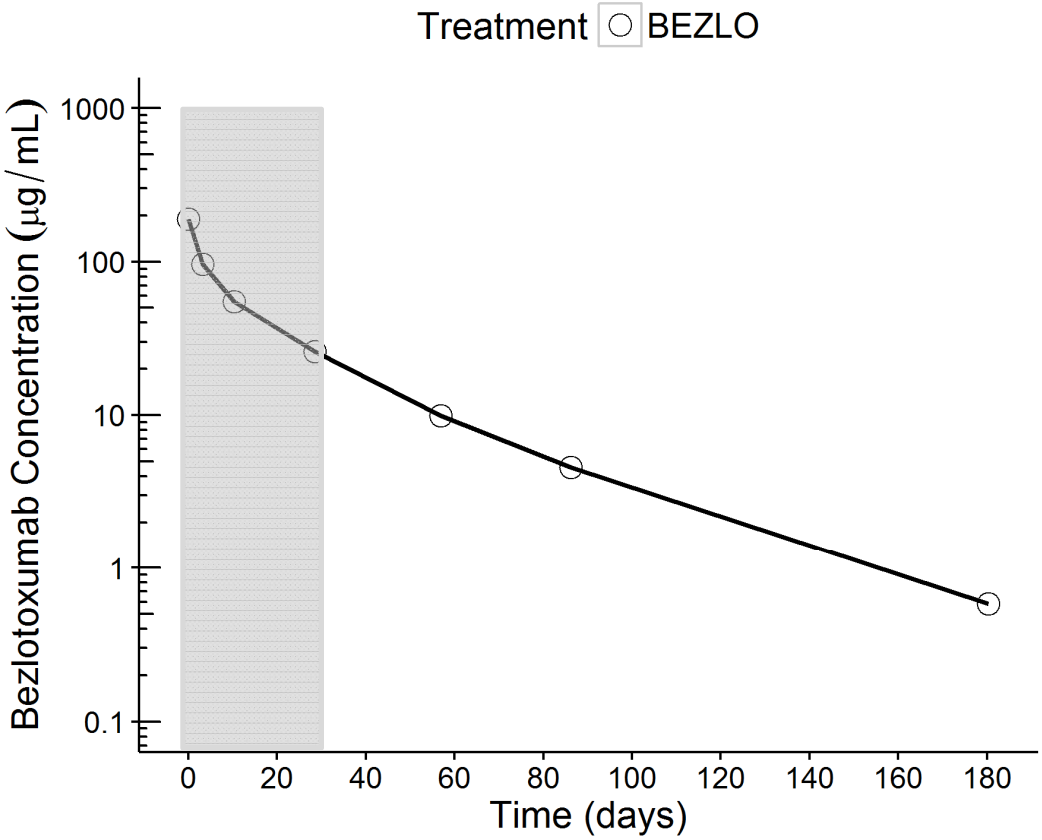
n=Number of subjects within subgroup that met the criteria for endpoint; m=Number of subjects within subgroup.
† Based on the Miettinen and Nurminen method without stratification.

# Recurrent CDI Characteristics - Laboratory (MODIFY I+II)

| | Placebo N=206 % (n/N) | BEZLO N=129 % (n/N) |
|---|---|---|
| Location of laboratory testing | | |
| + local/no central | 19.4 (40/206) | 11.6 (15/129) |
| + central/no local | 3.9 (8/206) | 5.4 (7/129) |
| + local/- central | 0.0 (0/206) | 2.3 (3/129) |
| + central/- local | 10.7 (22/206) | 15.5 (20/129) |
| + local/+ central | 66.0 (136/206) | 65.1 (84/129) |
| Local laboratory test method† | | |
| EIA | 45.5 (80/176) | 38.2 (39/102) |
| PCR | 47.2 (83/176) | 55.9 (57/102) |
| Cell Cytotoxicity Assay | 0.6 (1/176) | 1.0 (1/102) |
| Culture | 6.8 (12/176) | 4.9 (5/102) |

† Denominators for this category are those subjects who had a positive test at the local laboratory.
n=Number of subjects in the analysis population meeting the criteria.
N=Number of subjects included in the analysis population.
EIA=Enzyme Immunoassay; PCR=polymerase chain reaction, Culture = culture with toxin detection or with strain typing.

# Bezlotoxumab Present in Serum During Period of Greatest Risk for Recurrence

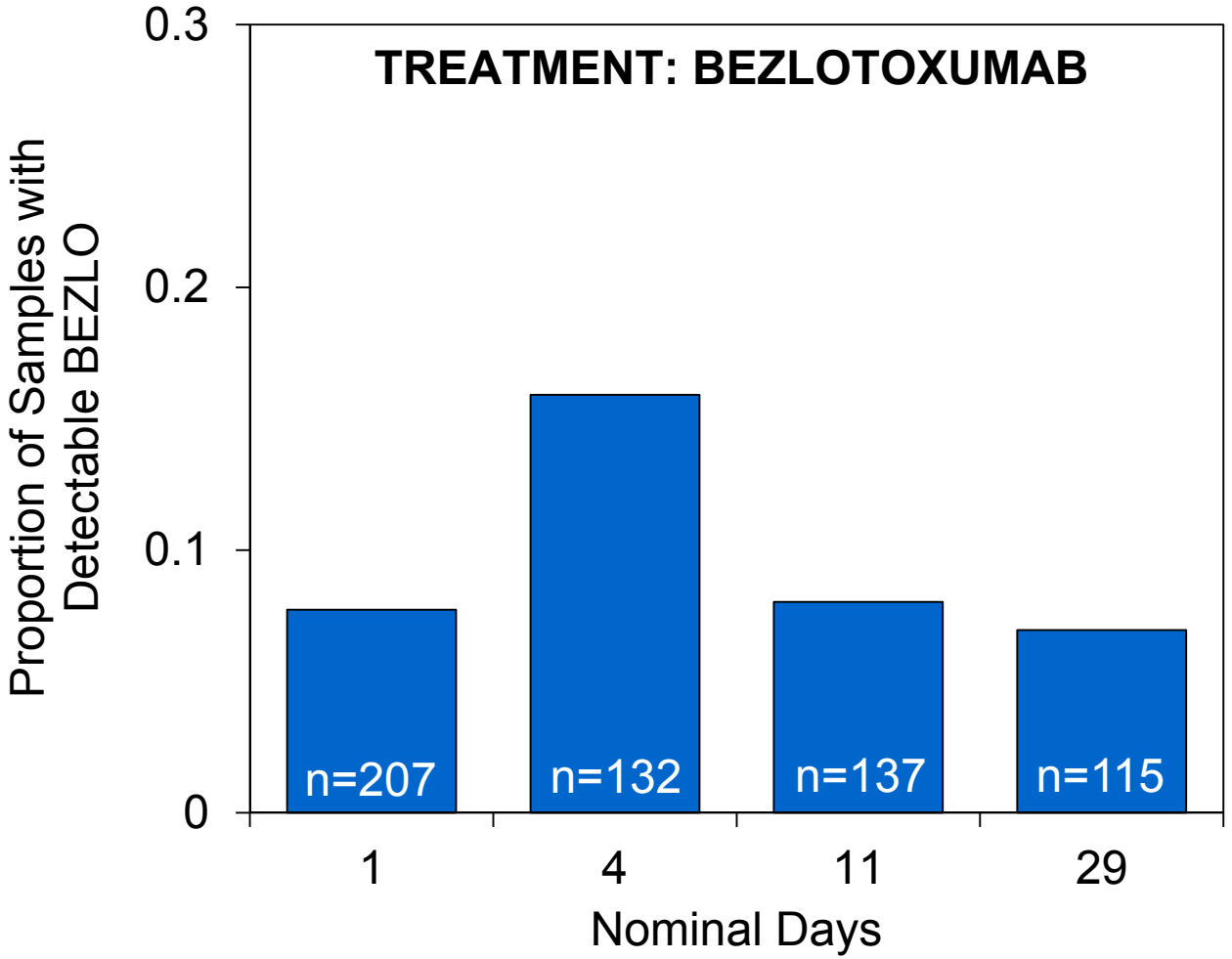



- Shaded region represents the time of highest risk of recurrence

# BEZLO Detection in Stool

- Goal of this analysis was to determine if systemic BEZLO can reach the intestinal lumen
- Of 396 subjects treated with BEZLO in MODIFY II, 256 (65%) provided stool samples after infusion
  - 724 stool samples analyzed – collected on Days 1, 4, 11 and 29, and at unscheduled visits
  - 67 samples had detectable BEZLO
- Assay semi-quantitative
  - Detected/not detected based on a threshold level

# Presence of BEZLO in Stool Supports Mechanism of Action



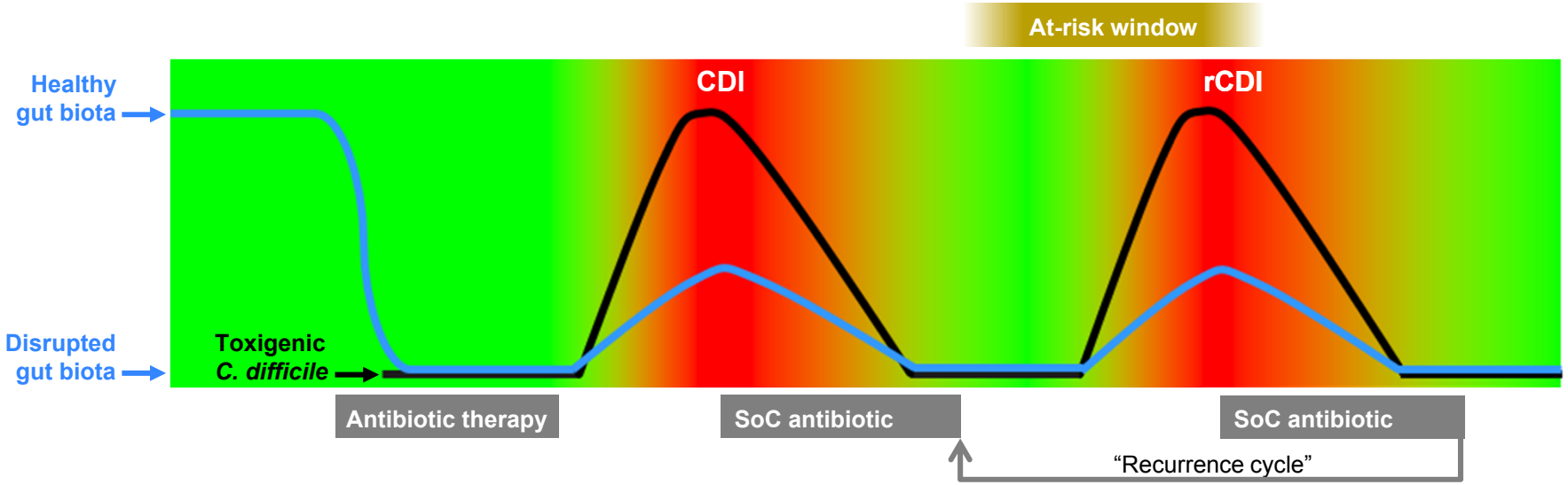

- BEZLO detected in stool samples of CDI patients as late as 29 days after treatment with BEZLO

# CDI Recurrence by Prior SoC Duration (MODIFY I+II)

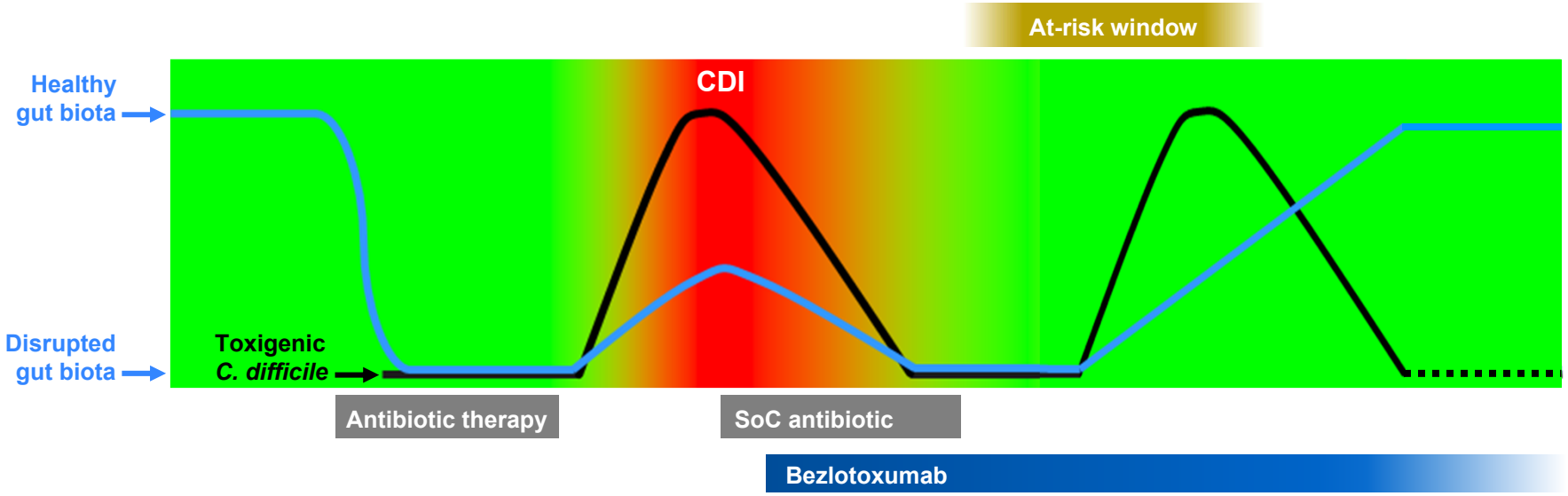
| | Placebo N=773 % (n/m) | BEZLO N=781 % (n/m) Difference (95% CI†) |
|---|---|---|
| SoC Start Relative to Infusion | | |
| 0-2 Days Prior‡ | 25.7 (85/331) | 15.7 (50/318)<br>-10.0 (-16.1, -3.7) |
| 3-4 Days Prior | 27.0 (62/230) | 15.9 (38/239)<br>-11.1 (-18.5, -3.7) |
| 5 or more Days Prior | 27.8 (59/212) | 18.3 (41/224)<br>-9.5 (-17.4, -1.6) |

† Based on the Miettinen and Nurminen method without stratification.
‡ Includes 1 subject who started SoC after infusion in the placebo group.
n=Number of subjects within subgroup that met the criteria for endpoint.
m=Number of subjects within subgroup.
SoC=Standard of Care.

# Bezlotoxumab Prevents Recurrent CDI During Period of Susceptibility



# Bezlotoxumab Prevents Recurrent CDI During Period of Susceptibility




Bezlotoxumab prevents clinical manifestation of CDI during at-risk window and allows microbiota to recover, leading to clearance of *C. difficile*