

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**761142Orig1s000**

**CLINICAL REVIEW(S)**

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

### CLINICAL REVIEW

|                                                                    |                                                                                                                                                                                                                     |
|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                                            | BLA                                                                                                                                                                                                                 |
| <b>Application Number(s)</b>                                       | 761142                                                                                                                                                                                                              |
| <b>Priority or Standard</b>                                        | Standard                                                                                                                                                                                                            |
| <b>Submit Date(s)</b>                                              | 6/11/19                                                                                                                                                                                                             |
| <b>Received Date(s)</b>                                            | 6/11/19                                                                                                                                                                                                             |
| <b>PDUFA Goal Date</b>                                             | 6/11/2020                                                                                                                                                                                                           |
| <b>Division/Office</b>                                             | Division of Neurology Products                                                                                                                                                                                      |
| <b>Reviewer Name(s)</b>                                            | Lawrence Rodichok MD                                                                                                                                                                                                |
| <b>Review Completion Date</b>                                      | 2/20/20                                                                                                                                                                                                             |
| <b>Established/Proper Name</b>                                     | Inebilizumab                                                                                                                                                                                                        |
| <b>(Proposed) Trade Name</b>                                       | Uplizna                                                                                                                                                                                                             |
| <b>Applicant</b>                                                   | Viela Bio                                                                                                                                                                                                           |
| <b>Dosage Form(s)</b>                                              | Intravenous                                                                                                                                                                                                         |
| <b>Applicant Proposed Dosing Regimen(s)</b>                        | Initial 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter, starting 6 months from the first infusion |
| <b>Applicant Proposed Indication(s)/Population(s)</b>              | Adults with neuromyelitis optica spectrum disorders (NMOSD)                                                                                                                                                         |
| <b>Recommendation on Regulatory Action</b>                         | Approval                                                                                                                                                                                                            |
| <b>Recommended Indication(s)/Population(s)<br/>(if applicable)</b> | The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive                                                                                 |

## Table of Contents

|                                                                                                                      |    |
|----------------------------------------------------------------------------------------------------------------------|----|
| Glossary.....                                                                                                        | 10 |
| 1. Executive Summary .....                                                                                           | 13 |
| 1.1. Product Introduction.....                                                                                       | 13 |
| 1.2. Conclusions on the Substantial Evidence of Effectiveness .....                                                  | 13 |
| 1.3. Benefit-Risk Assessment .....                                                                                   | 13 |
| 1.4. Patient Experience Data.....                                                                                    | 16 |
| 2. Therapeutic Context .....                                                                                         | 16 |
| 2.1. Analysis of Condition.....                                                                                      | 17 |
| 2.2. Analysis of Current Treatment Options .....                                                                     | 18 |
| 3. Regulatory Background .....                                                                                       | 19 |
| 3.1. U.S. Regulatory Actions and Marketing History.....                                                              | 19 |
| 3.2. Summary of Presubmission/Submission Regulatory Activity .....                                                   | 19 |
| 3.3. Foreign Regulatory Actions and Marketing History.....                                                           | 20 |
| 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on<br>Efficacy and Safety..... | 20 |
| 4.1. Office of Scientific Investigations (OSI) .....                                                                 | 20 |
| 4.2. Product Quality .....                                                                                           | 20 |
| 4.3. Clinical Microbiology .....                                                                                     | 20 |
| 4.4. Nonclinical Pharmacology/Toxicology .....                                                                       | 20 |
| 4.5. Clinical Pharmacology .....                                                                                     | 20 |
| 4.6. Devices and Companion Diagnostic Issues .....                                                                   | 20 |
| 4.7. Consumer Study Reviews .....                                                                                    | 21 |
| 5. Sources of Clinical Data and Review Strategy .....                                                                | 22 |
| 5.1. Table of Clinical Studies.....                                                                                  | 22 |
| 5.2. Review Strategy.....                                                                                            | 23 |
| 6. Review of Relevant Individual Trials Used to Support Efficacy .....                                               | 23 |

|                                                                                                                                                                                                                    |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 6.1. A Double-Masked, Placebo-Controlled Study With Open-Label Period To Evaluate The Efficacy And Safety of MEDI-551 In Adult Subjects With Neuromyelitis Optica And Neuromyelitis Optic Spectrum Disorders ..... | 23 |
| 6.1.1. Study Design.....                                                                                                                                                                                           | 23 |
| 6.1.2. Study Results.....                                                                                                                                                                                          | 34 |
| 7. Integrated Review of Effectiveness .....                                                                                                                                                                        | 61 |
| 7.1. Assessment of Efficacy Across Trials .....                                                                                                                                                                    | 61 |
| 7.1.1. Primary Endpoints.....                                                                                                                                                                                      | 61 |
| 7.1.2. Secondary and Other Endpoints .....                                                                                                                                                                         | 61 |
| 7.1.3. Subpopulations .....                                                                                                                                                                                        | 61 |
| 7.1.4. Dose and Dose-Response.....                                                                                                                                                                                 | 61 |
| 7.1.5. Onset, Duration, and Durability of Efficacy Effects .....                                                                                                                                                   | 61 |
| 7.2. Additional Efficacy Considerations.....                                                                                                                                                                       | 61 |
| 7.2.1. Considerations on Benefit in the Postmarket Setting .....                                                                                                                                                   | 61 |
| 7.2.2. Other Relevant Benefits.....                                                                                                                                                                                | 61 |
| 7.3. Integrated Assessment of Effectiveness .....                                                                                                                                                                  | 61 |
| 8. Review of Safety .....                                                                                                                                                                                          | 62 |
| 8.1. Safety Review Approach .....                                                                                                                                                                                  | 62 |
| 8.2. Review of the Safety Database .....                                                                                                                                                                           | 62 |
| 8.2.1. Overall Exposure .....                                                                                                                                                                                      | 62 |
| 8.2.2. Relevant characteristics of the safety population: .....                                                                                                                                                    | 65 |
| 8.2.3. Adequacy of the safety database: .....                                                                                                                                                                      | 67 |
| 8.3. Adequacy of Applicant's Clinical Safety Assessments.....                                                                                                                                                      | 67 |
| 8.3.1. Issues Regarding Data Integrity and Submission Quality .....                                                                                                                                                | 68 |
| 8.3.2. Categorization of Adverse Events.....                                                                                                                                                                       | 68 |
| 8.3.3. Routine Clinical Tests .....                                                                                                                                                                                | 68 |
| 8.4. Safety Results .....                                                                                                                                                                                          | 68 |
| 8.4.1. Deaths .....                                                                                                                                                                                                | 68 |
| 8.4.2. Serious Adverse Events.....                                                                                                                                                                                 | 71 |
| 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects .....                                                                                                                                               | 72 |
| 8.4.4. Significant Adverse Events.....                                                                                                                                                                             | 73 |

|                                                                       |     |
|-----------------------------------------------------------------------|-----|
| 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions .....  | 73  |
| 8.4.6. Laboratory Findings .....                                      | 78  |
| 8.4.7. Vital Signs .....                                              | 97  |
| 8.4.8. Electrocardiograms (ECGs).....                                 | 100 |
| 8.4.9. QT .....                                                       | 100 |
| 8.4.10. Immunogenicity .....                                          | 101 |
| 8.5. Analysis of Submission-Specific Safety Issues .....              | 101 |
| 8.5.1. Progressive Multifocal Leukoencephalopathy.....                | 101 |
| 8.5.2. Infections .....                                               | 104 |
| 8.5.3. Infusion-related reactions.....                                | 104 |
| 8.5.4. Immunosuppression .....                                        | 104 |
| 8.6. Safety Analyses by Demographic Subgroups .....                   | 105 |
| 8.7. Specific Safety Studies/Clinical Trials .....                    | 110 |
| 8.7.1. Study MI-CP200 .....                                           | 110 |
| 8.7.2. Study CD-IA-MEDI-551-1102.....                                 | 113 |
| 8.8. Additional Safety Explorations .....                             | 116 |
| 8.8.1. Human Carcinogenicity or Tumor Development.....                | 116 |
| 8.8.2. Human Reproduction and Pregnancy.....                          | 116 |
| 8.8.3. Pediatrics and Assessment of Effects on Growth .....           | 116 |
| 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....  | 116 |
| 8.9. Safety in the Postmarket Setting.....                            | 116 |
| 8.9.1. Safety Concerns Identified Through Postmarket Experience ..... | 116 |
| 8.9.2. Expectations on Safety in the Postmarket Setting .....         | 117 |
| 8.9.3. Additional Safety Issues From Other Disciplines .....          | 117 |
| 8.10. Integrated Assessment of Safety.....                            | 117 |
| 9. Advisory Committee Meeting and Other External Consultations.....   | 123 |
| 10. Labeling Recommendations .....                                    | 123 |
| 10.1. Prescription Drug Labeling .....                                | 123 |
| 10.2. Nonprescription Drug Labeling – N/A .....                       | 123 |
| 11. Risk Evaluation and Mitigation Strategies (REMS) .....            | 123 |

|                                                                                         |     |
|-----------------------------------------------------------------------------------------|-----|
| 12. Postmarketing Requirements and Commitments.....                                     | 123 |
| 13. Appendices .....                                                                    | 123 |
| 13.1. References .....                                                                  | 123 |
| 13.2. Financial Disclosure .....                                                        | 125 |
| 13.3. NMOSD Attack Criteria .....                                                       | 126 |
| 13.4. Schedule of Assessments – RCP .....                                               | 128 |
| 13.5. Schedule of Assessments – Attack Assessment Visit and Attack Follow-up Visit .... | 131 |
| 13.6. Schedule of Assessments during the Open Label Period .....                        | 133 |
| 13.7. Schedule of assessments during the Safety Follow-up Phase.....                    | 136 |
| 13.8. Narratives .....                                                                  | 136 |
| 13.8.1. SUBJECT (b) (6) .....                                                           | 136 |
| 13.8.2. SUBJECT (b) (6) .....                                                           | 138 |
| 13.8.3. Subject (b) (6) .....                                                           | 139 |

## Table of Tables

|                                                                                                                                                                |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Approved and commonly used unapproved treatments for NMOSD .....                                                                                      | 19 |
| Table 2: Number of subjects randomized by country .....                                                                                                        | 35 |
| Table 3: Disposition of randomized population, ITT .....                                                                                                       | 36 |
| Table 4: Important protocol violations/deviations, ITT .....                                                                                                   | 37 |
| Table 5: Demographics, ITT population .....                                                                                                                    | 38 |
| Table 6: Demographics of the AQP4 IgG seropositive subpopulation of the ITT .....                                                                              | 39 |
| Table 7: Baseline NMOSD characteristics .....                                                                                                                  | 41 |
| Table 8: Baseline EDSS score by strata, mITT .....                                                                                                             | 43 |
| Table 9: Number of relapses prior to randomization, by baseline AQP4-IgG status, mITT .....                                                                    | 43 |
| Table 10: Previous NMOSD maintenance therapy, by AQP4 baseline status .....                                                                                    | 43 |
| Table 11: Prior NMOSD Treatment, Medication Class, mITT .....                                                                                                  | 44 |
| Table 12: Prior NMOSD Treatment, Standard Medication Name, 10 most common, mITT .....                                                                          | 44 |
| Table 13: Comorbid conditions .....                                                                                                                            | 45 |
| Table 14: Medical history, by body system, 20% or more of either treatment group .....                                                                         | 45 |
| Table 15: Medical history standardized terms, 5% or more of either treatment group .....                                                                       | 46 |
| Table 16: Concomitant Medications during the RCP, Medication Class, most common, mITT ...                                                                      | 47 |
| Table 17: Concomitant Medications during the RCP, Standard Medication Name, most common, ITT .....                                                             | 47 |
| Table 18: Mean change in EDSS from baseline at attack visits .....                                                                                             | 48 |
| Table 19: Incremental change in EDSS from baseline at attack visits .....                                                                                      | 48 |
| Table 20: Criteria met for adjudication of attacks .....                                                                                                       | 48 |
| Table 21: Proportion of attacks meeting criteria, by total attacks and by treatment group .....                                                                | 49 |
| Table 22: Primary endpoint analysis by subgroups .....                                                                                                         | 53 |
| Table 23: Sensitivity analyses of the primary endpoint .....                                                                                                   | 53 |
| Table 24: Proportion of subjects meeting criteria for EDSS progression, by visit during the RCP                                                                | 55 |
| Table 25: Latest visit in the RCP by type of visit, mITT .....                                                                                                 | 55 |
| Table 26: Proportion of subjects who met criteria for EDSS progression at latest non-attack visit during the RCP, mITT .....                                   | 56 |
| Table 27: Proportion of subjects who met criteria for EDSS progression at latest non-attack visit during the RCP, anti-AQP4-IgG seropositive group, mITT ..... | 56 |
| Table 28: Proportion of subjects meeting criteria for EDSS progression, all visits, mITT .....                                                                 | 57 |
| Table 29: Proportion of subjects meeting criteria for EDSS progression, all visits, AQP4-IgG positive, mITT .....                                              | 57 |
| Table 30: Absolute change in EDSS at latest non-attack visit, mITT .....                                                                                       | 57 |
| Table 31: Percent change in EDSS at latest non-attack visit, mITT .....                                                                                        | 58 |
| Table 32: Change from baseline to last non-attack visit in Low-Contrast Visual Acuity binocular score .....                                                    | 58 |
| Table 33: Cumulative total active MRI lesions during the RCP .....                                                                                             | 58 |

|                                                                                                                                                                         |    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 34: Cumulative total active MRI lesions during the RCP, anti-AQP4 IgG seropositive subjects .....                                                                 | 59 |
| Table 35: Percent change from baseline to week 28 in the physical component score of the SF-36 .....                                                                    | 59 |
| Table 36: Change in NRS from baseline to last visit in RCT .....                                                                                                        | 59 |
| Table 37: Change from baseline to last non-attack visit in the modified Rankin Scale score .....                                                                        | 60 |
| Table 38: Annualized Relapse Rate, mITT .....                                                                                                                           | 60 |
| Table 39: Annualized Relapse Rate, anti-AQP4 seropositive subjects .....                                                                                                | 60 |
| Table 40: Number of subjects exposed to inebilizumab .....                                                                                                              | 62 |
| Table 41: Duration of Treatment during the RCP, years, safety population .....                                                                                          | 63 |
| Table 42: Duration of treatment, all inebilizumab population, safety population .....                                                                                   | 64 |
| Table 43: Duration of treatment, all inebilizumab population .....                                                                                                      | 64 |
| Table 44: Demographics, full safety population .....                                                                                                                    | 65 |
| Table 45: Demographics, safety population seropositive for anti-AQP4 IgG .....                                                                                          | 66 |
| Table 46: Serious Adverse Events during the RCP, by SOC and Preferred Term, safety population .....                                                                     | 71 |
| Table 47: Serious Adverse Events during the RCP, by SOC and Preferred Term, safety population, anti-AQP4 IgG seropositive subjects .....                                | 72 |
| Table 48: Adverse events that led to discontinuation of study drug, As Treated population .....                                                                         | 73 |
| Table 49: Treatment Emergent Adverse Events during RCP, Preferred Term, >2% of inebilizumab population, (greater than placebo shaded), safety population .....          | 73 |
| Table 50: Treatment Emergent Adverse Events during RCP, Preferred Term, >2% of inebilizumab population, (greater than placebo shaded), anti-AQP4 IgG seropositive ..... | 74 |
| Table 51: Treatment emergent adverse events during RCP, by SOC, Safety population .....                                                                                 | 75 |
| Table 52: Treatment emergent adverse events during the RCP, by SOC, anti-AQP4 IgG seropositive population .....                                                         | 76 |
| Table 53: Adverse events, Haematopoietic cytopenias SMQ, safety population .....                                                                                        | 77 |
| Table 54: Adverse events, drug related hepatic disorders SMQ, anti-AQP4 IgG safety population .....                                                                     | 77 |
| Table 55: ODE1 Adverse Event Groups by Treatment Group, 5% of more of the inebilizumab group, safety population .....                                                   | 78 |
| Table 56: Reduction in lymphocytes count by visit, any inebilizumab population, 120-day safety update .....                                                             | 80 |
| Table 57: CD19+ cells at baseline, mITT .....                                                                                                                           | 81 |
| Table 58: Percent change from baseline in CD19+ cell count at an attack visit .....                                                                                     | 84 |
| Table 59: CD19+ cell count by visit, treatment group and censor for unanimous AC-confirmed attack .....                                                                 | 84 |
| Table 60: Percent change from baseline in immunoglobulins at week 28 of the RCP .....                                                                                   | 90 |
| Table 61: Percent change from baseline, total immune globulins, by visit, all inebilizumab, mITT .....                                                                  | 91 |
| Table 62: Percent change from baseline in IgM levels, all inebilizumab group, by visit, mITT ....                                                                       | 91 |

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| Table 63: Percent change from baseline in anti-tetanus toxoid IgG at week 28 of the RCP.....            | 97  |
| Table 64: Blood pressure and Pulse rate .....                                                           | 98  |
| Table 65: QTcF during randomized treatment by actual treatment group.....                               | 100 |
| Table 66: ADA status, any time during RCP, mITT .....                                                   | 101 |
| Table 67: Proportion of subjects with any AE, by SOC, any inebilizumab population .....                 | 105 |
| Table 68: Adverse events by SOC, by ethnic group, any inebilizumab population .....                     | 106 |
| Table 69: Adverse events, by Region3, any inebilizumab population .....                                 | 107 |
| Table 70: SAEs by SOC and preferred term, any inebilizumab population .....                             | 117 |
| Table 71: SAEs, by SOC and preferred term, any inebilizumab population, 120-day safety<br>update.....   | 119 |
| Table 72: Adverse events, 5% or more of the any inebilizumab population .....                           | 121 |
| Table 73: Adverse events, 5% or more of the any inebilizumab population, 120-day safety<br>update ..... | 121 |

## Table of Figures

|                                                                                                                                                                                                                    |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 1: Time to first AC-confirmed attack, mITT.....                                                                                                                                                             | 50  |
| Figure 2: Time to first AC-confirmed relapse, AQP4-IgG positive subjects .....                                                                                                                                     | 51  |
| Figure 3: Time to first AC-confirmed relapse, AQP4-IgG negative subjects .....                                                                                                                                     | 52  |
| Figure 4: Duration of treatment, years, any inebilizumab population, safety population .....                                                                                                                       | 64  |
| Figure 5: Duration of treatment, years, any inebilizumab, anti-AQP4 IgG seropositive subjects .....                                                                                                                | 64  |
| Figure 6: Percent change from baseline, leukocyte count, by analysis visit, by actual treatment, RCP, safety population.....                                                                                       | 79  |
| Figure 7: Percent change from baseline, lymphocyte count, by analysis visit, by actual treatment, RCP, as treated population.....                                                                                  | 80  |
| Figure 8: CD19+ cells, mean percent change from baseline by visit, RCP, safety population.....                                                                                                                     | 82  |
| Figure 9: Mean CD19+ cell count by visit, mITT.....                                                                                                                                                                | 82  |
| Figure 10: Distribution of percent change from baseline in CD19+ cell count at attack visit .....                                                                                                                  | 83  |
| Figure 11: CD20+ cells, percent change from baseline by visit, RCP, as treated population .....                                                                                                                    | 85  |
| Figure 12: Percent reduction in CD20+ cells by visit and RCP treatment group .....                                                                                                                                 | 86  |
| Figure 13: Graphic Patient Profile, Subject (b) (6) .....                                                                                                                                                          | 88  |
| Figure 14: Hy's Law hepatotoxicity plot.....                                                                                                                                                                       | 89  |
| Figure 15: Total IgG, IgM, IgA, by analysis visit, any inebilizumab population, post-120-day update .....                                                                                                          | 93  |
| Figure 16: IgG by analysis visit, any inebilizumab population, post-120-day safety update.....                                                                                                                     | 94  |
| Figure 17: IgM by analysis visit, any inebilizumab population, post-120 day safety update .....                                                                                                                    | 95  |
| Figure 18: IgA by analysis visit, any inebilizumab population, post-120-day safety update .....                                                                                                                    | 96  |
| Figure 19: IgE by analysis visit, any inebilizumab population, post-120-day safety update .....                                                                                                                    | 97  |
| Figure 20: Systolic Blood pressure, percent change during infusion.....                                                                                                                                            | 99  |
| Figure 21: Diastolic blood pressure, percent change during infusion .....                                                                                                                                          | 100 |
| Figure 22: Sponsor Figure 11.4.1.1-1 Median Depletion and Dose-dependent Recovery of CD20 B Cells in Subjects After Single IV Dose of INEBILIZUMAB Through Day 337 (0.3 to 10.0 mg/kg; As-treated Population)..... | 111 |
| Figure 23: Sponsor Figure 11.4.1.1-1 Median Depletion and Recovery of CD20 B Cells following IV (x2) or SC Administration of inebilizumab .....                                                                    | 115 |

## Glossary

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|          |                                               |
|----------|-----------------------------------------------|
| AC       | advisory committee                            |
| ADA      | anti-drug antibody                            |
| ADCC     | antibody-dependent cellular cytotoxicity      |
| ADCP     | antibody-dependent cellular phagocytosis      |
| AE       | adverse event                                 |
| AESI     | adverse event of special interest             |
| ALT      | alanine aminotransferase                      |
| AQP4     | aquaporin-4                                   |
| AQP4-IgG | anti-aquaporin-4 antibody                     |
| AR       | adverse reaction                              |
| AST      | aspartate aminotransferase                    |
| BLA      | biologics license application                 |
| BMI      | body mass index                               |
| BPCA     | Best Pharmaceuticals for Children Act         |
| BRF      | Benefit Risk Framework                        |
| CBER     | Center for Biologics Evaluation and Research  |
| CDER     | Center for Drug Evaluation and Research       |
| CDRH     | Center for Devices and Radiological Health    |
| CDTL     | Cross-Discipline Team Leader                  |
| CFR      | Code of Federal Regulations                   |
| CI       | confidence interval                           |
| CMC      | chemistry, manufacturing, and controls        |
| CNS      | central nervous system                        |
| CRF      | case report form                              |
| CRO      | contract research organization                |
| CRT      | clinical review template                      |
| CTCAE    | Common Terminology Criteria for Adverse Event |
| CSF      | Cerebrospinal fluid                           |
| CSR      | clinical study report                         |
| CSS      | Controlled Substance Staff                    |
| DILI     | Drug-induced Liver Injury                     |
| DMC      | data monitoring committee                     |
| EC       | eligibility committee                         |
| ECG      | electrocardiogram                             |
| eCTD     | electronic common technical document          |
| EDSS     | Expanded Disability Status Scale              |

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Uplizna/inebilizumab

|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| EDV       | early discontinuation visit                                             |
| ETASU     | elements to assure safe use                                             |
| EU        | European Union                                                          |
| FDA       | Food and Drug Administration                                            |
| FDAAA     | Food and Drug Administration Amendments Act of 2007                     |
| FDASIA    | Food and Drug Administration Safety and Innovation Act                  |
| FSS       | Functional System Score                                                 |
| GCP       | good clinical practice                                                  |
| Gd        | gadolinium                                                              |
| GRMP      | good review management practice                                         |
| HR        | hazard ratio                                                            |
| ICF       | informed consent form                                                   |
| ICH       | International Council for Harmonization                                 |
| IDMC      | Independent Data Monitoring Committee                                   |
| IEC       | Independent Ethics Committee                                            |
| IGG       | Immunoglobulin G                                                        |
| IGM       | Immunoglobulin M                                                        |
| IND       | Investigational New Drug Application                                    |
| IRB       | Institutional Review Board                                              |
| ISE       | integrated summary of effectiveness                                     |
| ISS       | integrated summary of safety                                            |
| ITT       | intent to treat                                                         |
| IV        | intravenous                                                             |
| IVIG      | Intravenous Immune Globulin                                             |
| IVRS      | interactive voice response system                                       |
| IWRS      | interactive web response system                                         |
| LLN       | lower limit of normal                                                   |
| mAb       | monoclonal antibody                                                     |
| MCS       | mental component score                                                  |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| mITT      | modified intent to treat                                                |
| MOG       | myelin oligodendrocyte glycoprotein                                     |
| MRI       | magnetic resonance imaging                                              |
| mRS       | modified Rankin Scale                                                   |
| MS        | multiple sclerosis                                                      |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application                                                    |
| NME       | new molecular entity                                                    |
| NMO       | neuromyelitis optica                                                    |
| NMOSD     | neuromyelitis optica spectrum disorder                                  |
| NRS       | numeric rating scale                                                    |

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|       |                                            |
|-------|--------------------------------------------|
| OCS   | Office of Computational Science            |
| OLP   | open-label phase                           |
| ON    | optic neuritis                             |
| OPQ   | Office of Pharmaceutical Quality           |
| OSE   | Office of Surveillance and Epidemiology    |
| OSI   | opticospinal impairment scale              |
| OSI   | Office of Scientific Investigation         |
| OUS   | outside of the United States               |
| PBRER | Periodic Benefit-Risk Evaluation Report    |
| PC    | plasma cell                                |
| PCR   | polymerase chain reaction                  |
| PCS   | physical component score                   |
| PD    | pharmacodynamic                            |
| PI    | prescribing information or package insert  |
| PK    | pharmacokinetic                            |
| PLEX  | Plasma Exchange                            |
| PMC   | postmarketing commitment                   |
| PML   | Progressive Multifocal Leukoencephalopathy |
| PMR   | postmarketing requirement                  |
| PP    | per protocol                               |
| PPI   | patient package insert                     |
| PREA  | Pediatric Research Equity Act              |
| PRO   | patient reported outcome                   |
| PSUR  | Periodic Safety Update report              |
| PT    | preferred term                             |
| RAPD  | relative afferent pupillary defect         |
| RCP   | randomized controlled period               |
| REMS  | risk evaluation and mitigation strategy    |
| SAE   | serious adverse event                      |
| SAP   | statistical analysis plan                  |
| SGE   | special government employee                |
| SF-36 | Short Form-36 Health Survey                |
| SFP   | safety follow-up period                    |
| SOC   | standard of care                           |
| SOC   | system organ class                         |
| TB    | tuberculosis                               |
| TEAE  | treatment-emergent adverse event           |
| TESAE | treatment-emergent serious adverse event   |
| ULN   | upper limit of normal                      |
| US    | United States                              |

## 1. Executive Summary

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### 1.1. Product Introduction

Inebilizumab (previously known as MEDI-551) is a humanized, afucosylated IgG1 kappa monoclonal antibody that binds to the CD19 surface antigen on B-cells, including plasmablasts and some plasma cells. The effect of inebilizumab is mediated by both antibody-dependent cellular cytotoxicity and by antibody-dependent cellular phagocytosis. Inebilizumab does not mediate complement-dependent cytotoxicity (CDC). Inebilizumab is composed of 2 light chains and 2 heavy chains, with an overall molecular weight of approximately 149 kDa.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness in reducing attacks in patients with Neuromyelitis Spectrum Disorder (NMOSD) who were positive for Aquaporin-4 IgG AQP4-IgG antibody was demonstrated in a single randomized, placebo-controlled trial.

### 1.3. Benefit-Risk Assessment

### Benefit-Risk Integrated Assessment

In a single adequate and well-controlled trial conducted, there was a statistically significant benefit of inebilizumab treatment when measured by the time to the first relapse. Benefit is limited to NMOSD patients who are anti-AQP4 IgG seropositive. Although there were relatively few subjects who were anti-AQP4-IgG seronegative enrolled in the trial, there is no indication of a benefit in that subgroup. The evidence of benefit on reduction of relapses is robust and therefore reliance on a single trial can be justified in the setting of a rare disease. The serious disability caused by NMOSD relapses and the potential for a fatal outcome from acute cervical myelitis, the rarity of the condition, and the limited treatment options, also support approval based on a single adequate and well-controlled trial. Although analysis of some secondary endpoints is limited by the time-to-event design, these results are generally supportive of the primary analysis. An adequate proportion of subjects were from the US or North America. The characteristics of the subjects from outside the US and the results in those populations support translation of the overall results to the US population of NMOSD patients. The data on the safety of inebilizumab is adequate to support a positive benefit to risk comparison. However, there are very limited previous safety data on the use of inebilizumab in humans because the size and duration of the data from this single study is limited. Therefore, continued safety surveillance following approval will be important to an ongoing assessment of the benefit to risk comparison. The primary risk of treatment with inebilizumab, as with any therapy targeting B-cells, is the risk of infection. There was an observed decrease over time in patients' serum immunoglobulin levels in serum. The continued decline in immunoglobulin levels is a concern and should be monitored. Although there were no definite cases of PML in the study, there was one possible case, and therapies with presumed mechanisms of action similar to inebilizumab's have been associated with a risk of PML. Overall, the benefit to risk comparison justifies approval of the application.

### Benefit-Risk Dimensions

| Dimension                             | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                         | Conclusions and Reasons                                                                                     |
|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| <a href="#">Analysis of Condition</a> | <ul style="list-style-type: none"><li>• NMOSD is associated with recurrent attacks that predominantly involve the spinal cord and optic nerves</li><li>• NMOSD attacks can result in severe and largely irreversible neurologic disability, including loss of independent ambulation, loss of vision, and death from respiratory failure</li></ul> | Given the severity of many NMOSD attacks, a reduction in the occurrence of relapses is clinically relevant. |

| Dimension                                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons                                                                                                                                                                                                                                                                                  |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                           | <ul style="list-style-type: none"> <li>The spectrum of the severity of attacks in patients with NMOSD is uncertain. Although some attacks may be very severe, others may result in mild or moderate and reversible disability.</li> </ul>                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                          |
| <a href="#">Current Treatment Options</a> | <ul style="list-style-type: none"> <li>Soliris has recently been approved for the treatment of anti-AQP4-IgG seropositive NMOSD patients.</li> </ul>                                                                                                                                                                                                                                                                                                                   | The mechanism of action of Uplizna is distinct from that of Soliris and may, therefore, add an important alternative treatment for NMOSD. In addition, Uplizna would provide an alternative to patients who are allergic or unable to tolerate Soliris                                                   |
| <a href="#">Benefit</a>                   | <ul style="list-style-type: none"> <li>The time to the first adjudication committee-confirmed NMOSD relapse was significantly prolonged. This benefit is limited to anti-AQP4 IgG seropositive patients. There is relatively little uncertainty regarding this benefit. There is no indication of a benefit on short term disability. It is uncertain whether the reduction in relapses will translate to a benefit on longer-term irreversible disability.</li> </ul> | The demonstrated reduction in relapses is clinically relevant and offers a meaningful benefit to NMOSD patients.                                                                                                                                                                                         |
| <a href="#">Risk and Risk Management</a>  | <ul style="list-style-type: none"> <li>The available clinical data does not show a clear increased incidence of serious and opportunistic infections. However, the safety database is relatively limited. Therefore, there is significant uncertainty concerning the actual risk of infection. The progressive reduction in serum immunoglobulin levels is likely to increase the risk of infection if it continues over longer term treatment.</li> </ul>             | Long term surveillance for infections is necessary to ensure that the benefit continues to exceed the risk. The observed decrease and continued trend in decreased circulating immunoglobulin levels during the limited duration of observation in the trial merit further exploration in postmarketing. |

## 1.4. Patient Experience Data

### Patient Experience Data Relevant to this Application

|                                     |                                                                                                                                    |                                        |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| <input type="checkbox"/>            | The patient experience data that was submitted as part of the application include:                                                 | Section where discussed, if applicable |
| <input type="checkbox"/>            | Clinical outcome assessment (COA) data, such as                                                                                    |                                        |
| <input checked="" type="checkbox"/> | Patient reported outcome (PRO) – SF-36 and NRS for pain                                                                            | 6.1.2                                  |
| <input type="checkbox"/>            | Observer reported outcome (ObsRO)                                                                                                  |                                        |
| <input checked="" type="checkbox"/> | Clinician reported outcome (ClinRO) – modified Rankin Score                                                                        | 6.1.2                                  |
| <input type="checkbox"/>            | Performance outcome (PerfO)                                                                                                        |                                        |
| <input type="checkbox"/>            | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                        |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                        |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                        |
| <input type="checkbox"/>            | Natural history studies                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                        |
| <input type="checkbox"/>            | Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient experience data that were not submitted in the application, but were considered in this review:                            |                                        |
| <input type="checkbox"/>            | Input informed from participation in meetings with patient stakeholders                                                            |                                        |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                        |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                        |
| <input type="checkbox"/>            | Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient experience data was not submitted as part of this application.                                                             |                                        |

## 2. Therapeutic Context

## 2.1. Analysis of Condition

Neuromyelitis Optica (NMO) is an inflammatory disorder of the central nervous system characterized clinically by recurrent attacks that most commonly affect the optic nerves and spinal cord. Many clinicians originally considered NMO to be an unusually severe and limited form of Multiple Sclerosis (MS). When first recognized as a distinct clinical syndrome, a diagnosis of NMO, also known as “Devic’s syndrome”, was considered if acute bilateral optic neuritis and acute transverse myelitis occurred concurrently or within a short period of time of each other, typically resulting in near total loss of vision and/or paraplegia. Although NMO was originally considered a monophasic illness, it was recognized that relapses were seen in up to 90% of patients. In an early review of cases of NMO from the Multiple Sclerosis program at Mayo Clinic, Wingerchuk et al.<sup>1</sup> expanded the “strict” definition to include cases of bilateral optic neuritis and myelitis that had occurred within 2 years of each other, and in which there was no indication of disease elsewhere in the nervous system. The group meeting the strict criteria was compared to patients who did not meet these strict criteria but whose optic neuritis attack was unilateral and/or whose attacks occurred over a period of greater than 2 years. Of the 71 patients reviewed, 23 had had a “monophasic” course, i.e. qualifying attacks occurred over a median period of 5 days with no further attacks after a minimum period of 3 years follow-up, and 48 had a “relapsing” course, i.e. there were additional attacks. The clinical characteristics of these two groups did not differ. For the relapsing group, the next attack occurred within 1 year in 55%, within 3 years in 78% and within 5 years in 90%. The severity of the attacks appeared to be much worse in comparison to MS relapses. Functional blindness and permanent monoplegia or paraplegia were not uncommon on long-term follow-up. Respiratory failure due to cervical myelitis occurred in about one-third of relapsing patients resulting in death in 15/16 patients. NMO was also distinguished from MS by the relative absence of MRI changes in the brain. A cerebrospinal fluid (CSF) pleocytosis was more common in NMO patients and oligoclonal immunoglobulin bands in the CSF were typically absent. A phase of slowly progressive disability independent of relapses is common in MS but very uncommon in NMO where disability is largely due to incomplete recovery from the individual attacks<sup>2</sup>. In Asia, an “optico-spinal” form accounted for up to 40% of MS but was similar clinically to NMO<sup>3,4</sup>. Subsequent refinements in the diagnostic criteria for NMO were based on clinical and imaging features but distinction from MS was not reliable. However, an IgG antibody that was described initially by Lennon et al.<sup>5</sup> appears to be specific for patients with NMO. This antibody is not found in patients with MS. “NMO IgG” binds to aquaporin-4 (AQP4), the predominant water channel protein in the central nervous system (CNS). AQP4 is expressed prominently on astrocytic endfoot processes at the blood brain barrier in brain and spinal cord. It is also prominent in the subependymal region and in the floor of the 4th ventricle<sup>6</sup>. AQP4 immunoreactivity is not detectable in NMO lesions regardless of the stage of demyelination whereas this is the case only for inactive, usually chronic MS lesions. AQP4 immunoreactivity is increased at the perimeter of active areas of demyelination in MS. In NMO there may also be areas in the spinal cord and brainstem that show no evidence of demyelination but contain

eosinophil and plasma cell infiltrates with perivascular deposits of IgG, IgM and complement activation products<sup>6</sup>. This provides a rationale for the development of products that target either B cells or complement for the treatment of NMO. It is important to accurately distinguish NMO from MS because there are significant differences between NMO and MS in the approach to the treatment of acute attacks and the prevention of attacks. Furthermore, early intervention may be more critical for NMO because the prognosis for NMO has been considered much worse than that for MS.

The serum antibody to aquaporin 4 that appears to be specific for NMO and is found in most Japanese patients with opticospinal MS who meet the clinical criteria for NMO<sup>7</sup>. The sensitivity of the original indirect immunofluorescence assay in clinical NMO patients was 73% (95%CI: 60-86) and specificity was 91% (79-100%)<sup>7</sup>. For the Asian opticospinal MS, the sensitivity was 58% (30-86) and the specificity was 100% (66-100). There is wide variability in the sensitivity and specificity of the assays for anti-AQP4 antibody<sup>8</sup>. Some patients in whom the anti-AQP4 antibody is not found may test positive for an anti-myelin oligodendrocyte glycoprotein antibody (MOG). The clinical manifestations of CNS disease related to anti-MOG antibodies may be similar to that of NMOSD<sup>9</sup> but is increasingly described as an unique clinical disorder. The presence of the anti-AQP4 antibody is now a key criterion in the most recent criteria for the diagnosis of NMOSD<sup>10</sup>.

## 2.2. Analysis of Current Treatment Options

Prior to the approval of Soliris® on 6/27/19, there had been no approved treatments for NMOSD. Prior to that approval, drugs that had been approved for other indications and that targeted some aspect of the immune system that was perceived to be appropriate for the treatment of NMOSD were most commonly used for the treatment of NMOSD. The primary therapies used “off label” to treat NMOSD included rituximab, azathioprine, and mycophenolate. Rituximab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen. It is approved for the treatment of several autoimmune inflammatory disorders such as Rheumatoid Arthritis. Rituximab has been reported in uncontrolled studies to reduce the attack rate in NMOSD<sup>11-16</sup>. Following the initial treatment course, patients may be retreated when CD19+ cells (a marker for CD20 cells because the drug interferes with the assay for CD20 cells) reach a certain threshold indicating recover or for recurrent attacks. Safety concerns include those typical of most drugs that suppress the immune system along with serious infusion reactions, reactivation of hepatitis B virus and the possibility of progressive multifocal leukoencephalopathy (PML). Azathioprine (AZA) is a purine anti-metabolite approved for the treatment of RA. It has also been reported in uncontrolled studies to reduce the attack rate to nearly zero per year<sup>17,18</sup>. In addition to the risks due to immune suppression, AZA carries a black box warning for an increased risk of malignancies. Mycophenolate, an antimetabolite immunosuppressant generally used for suppression of rejection in transplant recipients, has also be used to prevent NMOSD relapses<sup>19,20</sup> with a relapse rate reduction comparable to that

with AZA and rituximab.

**Table 1: Approved and commonly used unapproved treatments for NMOSD**

| Product (s)<br>Name            | Relevant<br>Indication                                 | Year of<br>Approval | Route and<br>Frequency of<br>Administration                                                                                                       | Efficacy<br>Information                                 | Important<br>Safety and<br>Tolerability<br>Issues       | Other<br>Comments<br>(e.g.,<br>subpopulation<br>not addressed) |
|--------------------------------|--------------------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------|
| <b>FDA approved treatments</b> |                                                        |                     |                                                                                                                                                   |                                                         |                                                         |                                                                |
| Soliris                        | treatment<br>AQP4<br>positive<br>(NMOSD)<br>in adult s | 2019                | 900 mg IV<br>weekly X 4,<br>followed by 1200<br>mg for the 5 <sup>th</sup><br>dose one week<br>later, then 1200<br>mg every 2<br>weeks thereafter | Reduction<br>by 96% in<br>Annualized<br>Relapse<br>Rate | Black box<br>warning for<br>meningococcal<br>infections |                                                                |
| <b>Other Treatments</b>        |                                                        |                     |                                                                                                                                                   |                                                         |                                                         |                                                                |
| Rituximab                      | RA, GPA,<br>MPA, PV*                                   | 1997                | 375 mg/m <sup>2</sup> IV<br>qweek X4                                                                                                              | No<br>controlled<br>trials                              | Infection,<br>infusion<br>reactions                     |                                                                |
| Azathioprine                   | RA                                                     | 1968                | 100 mg po qd                                                                                                                                      | No<br>controlled<br>trials                              | Infection,<br>malignancy                                |                                                                |
| Mycophenolate                  | Transplant<br>rejection                                | 1995                | 1000 mg/day                                                                                                                                       | No<br>controlled<br>trials                              | Infection,<br>malignancy                                |                                                                |

\*: RA: Rheumatoid arthritis, GPA: Granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PV: pemphigus vulgaris

### 3. Regulatory Background

#### 3.1. U.S. Regulatory Actions and Marketing History

Orphan Status: 2/10/16 (15-904)

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND meeting: 5/20/13

May Proceed: 2/27/14

SPA No Agreement: 3/17/14

SPA No Agreement meeting: 6/5/14

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

Orphan Status: 2/10/16 (15-904)  
Pre-BLA meeting: 2/19/19  
Grant Breakthrough Therapy Designation: 4/17/19

The sponsor submitted a Type C meeting request in November, 2016. The answers to questions posed in the meeting request were answered by email.

### **3.3. Foreign Regulatory Actions and Marketing History**

No approvals outside of the United States

## **4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### **4.1. Office of Scientific Investigations (OSI)**

Three sites were inspected: Drs. Cree, Pardo-Villamizar, and Villegas. There were no significant findings.

### **4.2. Product Quality**

See the reviews by the CMC reviewers

### **4.3. Clinical Microbiology**

See the review by the microbiology reviewer

### **4.4. Nonclinical Pharmacology/Toxicology**

See the review by Dr. Wilcox

### **4.5. Clinical Pharmacology**

See the review by Dr. Dawei Li

### **4.6. Devices and Companion Diagnostic Issues**

Identification of the anti-AQP4 IgG antibody is necessary to select a population with NMOSD that will benefit from treatment with inebilizumab. The assay employed to qualify subjects for this study, performed at (b) (4) has not been cleared for marketing by the Center for

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

Devices and Radiological Health (CDRH). At the time of this review, one such device/assay has been cleared by CDRH, namely the KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay. This was cleared through the de novo pathway under DEN 150030.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K161951>

#### **4.7. Consumer Study Reviews**

There were no consumer study reviews

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

| Trial Identifier                                                                                            | Design                 | Dose regimen                                          | Endpoints                                                                                                         | Treatment duration          | Number treated              | Population                        |
|-------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------------|
| <b>Controlled Clinical Studies</b>                                                                          |                        |                                                       |                                                                                                                   |                             |                             |                                   |
| CD-IA-MEDI-551-1155                                                                                         | Placebo-controlled RCT | 300 mg IV inebilizumab or placebo on Day 1 and Day 15 | <u>Primary</u> : Time (days) from Day 1 to the onset of an AC-determined NMOSD attack on or before the end of RCP | To first relapse or Day 197 | MEDI551: 174<br>Placebo: 56 | NMOSD, AQP4 positive and negative |
| <b>Studies to Support Safety</b>                                                                            |                        |                                                       |                                                                                                                   |                             |                             |                                   |
| CD-IA-MEDI-551-1155 OLE                                                                                     | Open label extension   | 300 mg IV inebilizumab every 26 weeks                 | Safety                                                                                                            | Variable                    | 225                         | Relapse or completed RCP          |
| MI-CP200                                                                                                    | SAD                    | See 1                                                 | Safety                                                                                                            | Single dose                 | MEDI-551: 28<br>Placebo: 4  | Scleroderma                       |
| CD-IA-MEDI-551-1102                                                                                         | SAD                    | See 2                                                 | Safety                                                                                                            | Single dose                 | MEDI-551: 21<br>Placebo: 7  | RMS                               |
| <b>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</b> |                        |                                                       |                                                                                                                   |                             |                             |                                   |
| No other clinical studies                                                                                   |                        |                                                       |                                                                                                                   |                             |                             |                                   |

SAD: Single Ascending Dose; RMS: Relapsing forms of Multiple Sclerosis

1: 0.1 mg/kg [n = 1], 0.3 mg/kg [n = 4], 1.0 mg/kg [n = 6], 3.0 mg/kg [n = 6], and 10.0 mg/kg [n = 7]

2: 30 mg IV [n = 6], 60 mg SC [n = 3], 100 mg IV [n = 3], 100 mg SC [n = 3], and 600 mg IV [n = 6]

## 5.2. Review Strategy

This review relies on a thorough review of the single clinical trial for efficacy and the safety data from both the randomized controlled phase (RCP) of the study and the open label extension phase following the RCP.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. A Double-Masked, Placebo-Controlled Study With Open-Label Period To Evaluate The Efficacy And Safety of MEDI-551 In Adult Subjects With Neuromyelitis Optica And Neuromyelitis Optic Spectrum Disorders

#### 6.1.1. Study Design

##### Overview and Objective

This study was a double-blind, placebo-controlled, randomized trial in which eligible patients with NMOSD were randomized 3:1 to treatment with inebilizumab or placebo. The primary objective was to demonstrate that treatment with inebilizumab was superior to placebo in the reduction of protocol-defined NMOSD attacks. Enrollment was to continue until one of the following occurred:

- A total of 67 Adjudication Committee (AC)-determined NMOSD attacks had occurred
- 252 subjects had been randomized and dosed
- Recommendation by the independent DMC to cease enrollment

##### Trial Design

##### Methods of Blinding and Reduction of potential bias

Sponsor staff, investigators, health care professionals involved in the care of subjects, and the subjects themselves were to be unaware of treatment assignment. Both treatment groups received the same pre-treatment regimen prior to administration of inebilizumab or placebo. The placebo consisted of the components of the vehicle used for the active drug. Blinding was maintained for those subjects who transitioned to the Open Label Phase (OLP) of the trial.

The EDSS, visual function, and MRI assessments that were used in the determination of whether a protocol-defined attack had occurred were performed by qualified individuals who were not aware of treatment assignment and were not involved in the care of subjects. MRI scans were not reviewed by the investigator or the Adjudication Committee until all clinical

assessments were completed and reviewed.

### Eligibility

Patients were assessed for eligibility during the 28-day screening phase. Patients who did not meet all of the eligibility criteria were permitted to be rescreened once, including those who experienced an attack during screening. An independent Eligibility Committee evaluated the clinical data for patients who were seronegative for the Aquaporin-4 IgG antibody to determine whether they met the 2006 clinical criteria for NMO<sup>21</sup>.

#### Key Inclusion criteria:

1. Age 18 years or older
2. NMOSD based on one of the following:
  - a. Positive serum anti-AQP4-IgG result at screening (verified by the allocated central laboratory) and a documented history of one or more NMO/NMOSD acute relapses that required rescue therapy within the last year, or 2 or more NMO/NMOSD acute relapses that required rescue therapy within 2 years prior to screening
  - b. Negative serum anti-AQP4-IgG result at screening (verified by the allocated central laboratory) without evidence of brain lesion consistent with MS and meets the clinical criteria for NMO according to Wingerchuk et al, 2006<sup>22</sup> and a documented history of one or more NMO acute relapses that required rescue therapy within the last year, or 2 or more NMO acute relapses that required rescue therapy within 2 years prior to screening. Note that data from AQP4-IgG seronegative subjects were reviewed by an independent eligibility committee to confirm eligibility.
3. Patients who have had a relapse immediately prior to screening must have had at least 4 weeks in which their relapse symptoms were stable or improving prior to randomization.
4. Expanded Disability Status Scale score at randomization less than or equal to 7.5. A score of 8.0 was eligible if the investigator and medical monitor assessed that the subject was reasonably able to participate in the study

#### Key Exclusion criteria:

1. An estimated glomerular filtration rate (GFR) of < 60 mL/minute
2. CD19+ B cell counts below the lower limit of normal (LLN) according to the central laboratory
3. Receipt of the following at any time prior to randomization:

- a. Alemtuzumab
  - b. Total lymphoid irradiation
  - c. Bone marrow transplant
  - d. T-cell vaccination therapy
4. Receipt of rituximab or any experimental B-cell depleting agent within the 6 months prior to screening, unless the subject had B-cell counts above the LLN according to the central laboratory
5. Receipt of IVIG within 1 month prior to randomization
6. Receipt of any of the following within 3 months prior to randomization:
  - a. Natalizumab (Tysabri®)
  - b. Cyclosporin
  - c. Methotrexate
  - d. Mitoxantrone
  - e. Cyclophosphamide
  - f. Tocilizumab
  - g. Eculizumab
7. Anti-AQP4-IgG seronegative subjects with a brain MRI abnormality that met the diagnostic criteria for MS (MRIs taken at screening were assessed centrally)
8. Any concomitant disease other than NMO that required treatment with oral or IV steroids at doses > 20 mg/day for > 21 days within the 6 months prior to screening
9. Any subjects diagnosed with a concurrent autoimmune disease that was either uncontrolled or required the use of disease-modifying agents or immunosuppressive agents
10. Receipt of any of the following:
  - a. Any live or attenuated vaccine within 3 weeks prior to Day 1 (administration of killed vaccines was acceptable; the Sponsor recommended that investigators ensure all subjects were up to date on required vaccinations prior to study entry)
  - b. Bacillus of Calmette and Guérin (BCG) vaccine within 1 year of signing the ICF
  - c. Blood transfusion within 4 weeks prior to signing the ICF
11. Clinically significant serious active or chronic viral or bacterial infection that requires treatment with anti-infectives, hospitalization, or, in the investigator's opinion, represented an additional risk to the subject, within 60 days prior to randomization
12. Known history of a primary immunodeficiency (congenital or acquired) or an underlying condition such as human immunodeficiency virus (HIV) infection or splenectomy that predisposes the subject to infection

13. At screening (one repeat test may be conducted to confirm results prior to randomization within the same screening period), any of the following:
  - a. Total Ig < 600 mg/dL
  - b. Absolute neutrophil count < 1200 cells/ $\mu$ L
  - c. CD4 T lymphocyte count < 300 cells/ $\mu$ L
14. Confirmed positive test for hepatitis B/hepatitis C serology at screening:
  - a. Hepatitis B surface antigen positive,
  - b. Hepatitis B core antibody positive with negative hepatitis B surface antibody
  - c. Hepatitis C antibody positive
15. Subjects with a positive QuantiFERON<sup>®</sup>-TB Gold test, unless an appropriate course of anti-tuberculosis (TB) treatment has been documented. Subjects with an indeterminate result may be eligible if a chest x-ray shows no evidence of TB and there was no evidence of latent TB
16. History of cancer, apart from squamous cell or basal cell carcinoma of the skin treated with documented success of curative therapy > 3 months prior to randomization

#### Randomization

Two-hundred fifty-two (252) eligible patients were to be randomized 3:1 to inebilizumab or placebo and Day 1. Randomization was stratified for anti-AQP4 IgG serostatus (targeting a ratio of 80:20 for positive:negative status) and for region (Japan; non-Japan). Enrollment was to continue until 67 Adjudication Committee (AC)-confirmed attacks had occurred.

#### Randomized-controlled Period (RCP)

The period of blinded treatment was to continue for up to 197 days or until an AC-confirmed attack occurred. Assessments conducted during the RCP are listed in Appendix [13.4](#).

#### Identification of attacks

Potential attacks may have come to attention of study investigators because of a direct subject report, at a regularly scheduled visit, or during biweekly phone calls to subjects made beginning on day 43. Subjects were instructed to notify the site of new or worsening symptoms as soon as possible. If the symptoms seemed to represent an attack, an assessment visit was to be scheduled within 72 hours of the report. If the symptoms were deemed by the investigator to be related to NMOSD, then a sequence of assessments was required to be completed within 5 days. The exact sequence of assessments was determined by the type of attack that might be occurring. The types of potential attacks and their criteria are detailed in Appendix [13.3](#). Clinical assessments preceded the MRI scan in all cases. The assessments conducted at this visit are

listed in Appendix 13.5 Any symptoms determined to be unrelated to NMOSD were to be reported as adverse events. If the event met one of the Attack Criteria, then the subject was considered to have completed the RCP and was offered enrollment in the Open Label Phase. Investigators were encouraged to not institute acute treatment for the attack until the necessary assessment were completed. If deemed necessary, acute treatment with IV corticosteroids, intravenous immunoglobulin, and/or plasma exchange, could be initiated at any time. If the event was determined to not meet the criteria, then the subject was to continue in the RCP. Any subject reports that were determined by the investigator to not represent a potential attack were, nevertheless, provided to the AC for review.

#### Adjudication of attacks

The Adjudication Committee (AC) was to complete the process within 14±3 days of the start of the Assessment Visit.

The data set that was delivered to the AC was identical to the data set generated and used by the Principal Investigator to make the diagnosis of NMO/NMOSD attack and included the following:

- Description of the new or worsening symptom
- Findings of physical and neurological examination
- Relevant laboratory test results
- Relevant x-ray studies, if performed in relation to the assessment
- Expanded Disability Status Scale score as determined by the independent assessor
- Ophthalmology examination results done by an independent ophthalmologist
- Magnetic resonance imaging scans if done as required by certain protocol attack criteria
- Short narrative written by the Principal Investigator to summarize the assessment WITHOUT disclosing if an NMO/NMOSD attack was diagnosed (narrative template will be provided by the Sponsor)

*Reviewer Comment: The AC was blinded to treatment assignment and to any laboratory results that might suggest treatment assignment (e.g. B-cell counts and anti-AQP4 IgG titers).*

An Attack follow-up assessment was conducted for all attacks that were determined to meet the protocol-defined criteria by the investigator, regardless of the adjudication result.

Assessments conducted at the Attack Follow-up visit are listed in Appendix 13.5.

Subjects who completed the RCP, including those who completed because of an AC-adjudicated attack, and subjects participating in the RCP at the time the study was terminated were offered

the option to enroll in the Open Label Phase (OLP) of the trial.

Subjects were given the option to enter the OLP if they:

- Completed 197 days of the RCP
- Experienced an AC-determined NMO/NMOSD attack during the RCP
- Were in the RCP at the time when 67 AC-determined attacks had occurred
- Were in the RCP when enrollment is discontinued upon recommendation of the DMC based on evidence of efficacy and safety

Subjects who discontinued from the RCP for reasons other than one of the reasons above were not eligible for the OLP. The OLP was to start within 14 days of completion of the RCP. The OLP was to continue for a minimum of one year and a maximum of 3 years after the last subject was randomized or until the drug was approved in the local jurisdiction.

Assessments conducted during the OLP are listed in Appendix 13.6.

Subjects who discontinued prematurely from either the RCP or the OLP were to enter a Safety Follow-up Phase (SFP). The duration of the SFP was 12 months from the last dose of inebilizumab. Assessments conducted during the SFP are listed in Appendix 13.7.

#### Aquaporin IgG serostatus assay

The assay for the presence of anti-aquaporin 4 IgG antibody used as one of the criteria to assess eligibility was determined at the (b) (4) using a modification of a commercially available EUROIMMUN assay. To determine the titer of AQP4-IgG a quantitative flow cytometry method based on binding to cells transfected with AQP4 was used.

*Reviewer Comment: The sponsor confirmed that neither the EUROIMMUN nor (b) (4) modification of the EUROIMMUN assay used in the study have been cleared by CDRH.*

#### Treatment

Rationale: A dose of 300 mg of inebilizumab was expected to achieve nearly complete depletion of B-cells. Subjects were treated with either 300 mg IV inebilizumab or matching placebo on Study Days 1 and 15. Investigational product was administered as a 90-minute IV infusion via an infusion pump.

All subjects in the placebo and inebilizumab arms were premedicated on Day 1 and Day 15 with IV methylprednisolone (80-125 mg or equivalent glucocorticoid), oral diphenhydramine (25-50 mg or equivalent antihistamine), and oral paracetamol (acetaminophen; 500-650 mg)

prophylactically to prevent infusion reactions.

Additionally, all subjects entering the RCP were treated for 2 weeks (Day 1 to Day 14) with oral corticosteroids (prednisone 20 mg/day or equivalent oral glucocorticoid). A tapering schedule was implemented from Day 15 to Day 21. Subjects with signs or symptoms of a clinically significant infection at the time of the planned infusion of inebilizumab or placebo were not to be treated until the infection had resolved. A physician had to be present at the site or immediately available to respond to emergencies during all administrations of inebilizumab or placebo. Fully functional resuscitation facilities had to be available.

#### Concomitant medications

The following medications and procedures were prohibited from the day of dosing on Day 1 through the end of the subjects' participation in the OLP:

- Any immunosuppressant for the prevention of NMO/NMOSD attacks
- High-dose corticosteroids, with the exception of those required to treat an NMO/NMOSD attack
- Low-dose corticosteroids, unless discussed and agreed with the medical monitor, with the exception of those specified by the protocol in the RCP and topical steroids
- Plasma exchange, unless used to treat an NMO/NMOSD attack.
- Alemtuzumab
- Eculizumab
- Total lymphoid irradiation
- Bone marrow transplant
- T-cell vaccination therapy
- Natalizumab
- Cyclosporin
- Methotrexate
- Mitoxantrone
- Cyclophosphamide
- Tocilizumab
- Any other immunosuppressant medication, unless discussed and approved by the medical monitor

*Reviewer Comment: Subjects were allowed to continue immunosuppressants during screening as long as the dose remained stable or was being decreased.*

#### Study Endpoints

The primary endpoint was the time (days) from Day 1 to the onset of an AC-determined NMOSD attack on or before the end of RCP (Day 197/discontinuation visit).

Endpoints 1, 2, 3, and 4 are key secondary endpoints considered for Type I error control.

1. Worsening from baseline in EDSS at last visit during the RCP.  
A subject is considered to have a worsening in overall EDSS score if one of the following criteria is met:
  - a. Worsening of 2 or more points in EDSS score for subjects with baseline score of 0.
  - b. Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5.
  - c. Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.
2. Change from baseline in low-contrast visual acuity binocular score as measured by low-contrast Landolt C Broken Rings Chart, at last visit during the RCP.
3. Cumulative total active MRI lesions (new Gadolinium-enhancing or new/enlarging T2) during the RCP.
4. Number of NMOSD-related in-patient hospitalizations. In-patient hospitalization is defined as more than an overnight stay
5. Annualized attack rate (total number of AC-determined NMO/NMOSD attacks normalized by person-years) during any exposure to inebilizumab.

### Statistical Analysis Plan

The study was designed to control the overall Type I error rate of  $\alpha = 0.05$  based on the Bonferroni-based chain procedure. The primary null hypothesis is to be hierarchically tested first at  $\alpha = 0.05$  in the anti-AQP4 IgG seropositive cohort, and, if significant, it is to be further tested in the ITT population (subjects who received any dose of IP regardless of anti-AQP4 IgG status) at  $\alpha = 0.05$ . If and only if the treatment group comparison is statistically significant within the ITT population, secondary hypotheses will be tested. Null hypotheses for the 4 key secondary endpoints follow the same sequential testing strategy as the primary analysis (testing within seropositive subjects first, followed by the ITT population if the comparison within seropositive subjects is statistically significant).

### Primary Analysis

The primary analysis of time to AC-determined attack estimated the hazard ratio using the Cox proportional hazard model. Onset day was defined as the study day that the subject visited the site for possible attack assessment (i.e., the initiation of attack assessment visit). Only AC-determined attacks with an assessment visit scheduled within 120 hours (5 days) of reporting symptoms and all necessary assessments done within 10 days of an Assessment Visit were included in the primary analysis. Other AC-determined attacks not included in primary analysis

were included in other supportive analyses. No imputation was performed for missing data for primary analysis. Subjects who completed the Day 197 visit of the RCP or who discontinued the study before Day 197 for reasons other than an AC-determined NMO/NMOSD attack have been censored in this model at the time of the Day 197/discontinuation visit.

Missing values of the secondary efficacy endpoints due to dropout or missing data were handled as follows:

1. For worsening from baseline in EDSS endpoint, missing values was considered as 'worsening' according to non-responder imputation (NRI) rule.
2. For low-contrast visual acuity endpoint, the last non-missing value was considered for analysis.

*Reviewer Comment: The assumption is made that if EDSS values are missing then there was no progression of disability.*

The sponsor submitted a Type C meeting request in November, 2016, to discuss the conduct of a planned Sample Size Reassessment (SSR) when the 198<sup>th</sup> subject was randomized, at which point the sponsor anticipated that 75% of the planned subjects would have completed the RCP. The SSR would be conducted at a time point unrelated to the timing of the planned futility analysis. The Division advised that the SSR should precede the futility analysis. The sponsor subsequently proposed to increase the sample size to 252 subjects without a formal SSR. The Division was in agreement with that proposal.

In January, 2017, the Division received from the sponsor the minutes of the most recent IDMC meeting on January 13, 2017. The sponsor indicated that 212 subjects had been randomized as of January 9, 2017. As of the data cutoff, the AC had confirmed 38 NMO/NMOSD attacks among 34 subjects. Six (6) of the attacks occurred in the open-label period (OLP) in 5 subjects. The 2 treatment groups were identified as groups A and B. The estimated Hazard ratio based on the data as of the cut-off point was 0.18 (0.08, 0.38) and the conditional power to predict a statistically significant difference between groups A and B was >99.9%.

*Reviewer Comment: Because randomization ratio was 3:1, the identity of the group treated with inebilizumab was obvious and therefore, since the initial IDMC meeting, it is likely that members were aware of the primary analysis result and that the sponsor became aware, at the latest, at the time of the interaction described above.*

## Protocol Amendments

First patient enrolled: January 6, 2015

Last treatment start date: 9/18/18

Amendment 1: June 16, 2014

1. The following changes were made: 1) Revised the timeframe of the primary endpoint definition from Day 183 to Day 197 to coincide with the increased length of the RCP, which was extended by 2 weeks to account for the 2-week oral corticosteroid use between Day 1 and Day 14; 2) Removed the restriction that the primary analysis will be based on AQP4-IgG seropositive subjects. The primary analysis will first be tested in AQP4-IgG seropositive subjects, and if statistically significant, it will be further tested in all subjects
2. Revised the subject population for the primary analysis to include both AQP4-IgG seropositive and seronegative subjects.
3. Revised the visual acuity endpoint to change the measurement tool from the Sloan Letters Low Contrast Chart to the Landolt C Broken Rings Chart as recommended; Added an MRI lesion endpoint to coincide with the addition of a secondary objective; Revised the definition of in-patient hospitalization from hospital stay greater than 24 hours to more than an overnight stay.
4. Changed the sample size of the study from 252 to 212 subjects due to the addition of the AQP4-IgG seronegative subjects as part of the primary endpoints, with the potential to increase the number of subjects to 252 if the sample size needed to be reassessed; Extended the RCP to 197 days to account for the 2-week oral corticosteroid use between Day 1 and Day 14;
5. For subjects completing Day 197 of the RCP, Day 1 of the OLP will be the same day, but may be delayed up to 14 days without repeating procedures; subjects will not be permitted to enter the OLP after 14 days.
6. Revised text to inform that data from all subjects who are assessed at an Assessment Visit will be sent for adjudication by the AC regardless of whether the Principal Investigator has determined that an NMO/NMOSD attack has occurred;

Amendment 2: December 15, 2015

1. Text was revised to clarify that assessment of new symptoms or worsening of existing symptoms should be completed within 5 days to determine if an attack has occurred.
2. Text was revised to clarify that the study was event driven and enrollment of subjects would stop when a total of 67 AC-determined NMOSD attacks had occurred. The planned number of subjects to be enrolled was 212; however, based on sample size reassessment the number may be increased to a maximum of 252 subjects.
3. Text was added to clarify that Day 1 is to occur within 28 days of the start of the screening period.
4. Adjudication Process (For Attacks Occurring During the RCP): Text was revised to clarify that the AC process will be completed when the AC makes the final decision and that this will occur within a total of 14 days (+ 3 days) from the start of the Assessment Visit and that the

data set will be provided to the independent AC by the vendor.

5. Text was added to clarify that the ophthalmology examiner is also independent and not otherwise involved in evaluating or examining the subject outside of the protocol to reduce the potential for bias
6. Text was revised to clarify that the EDSS assessment must be conducted by a trained and certified neurologist who is also independent of the treating physician and the subject to reduce the potential for bias.
7. Text was revised to clarify that immunosuppressive medications must be stopped prior to dosing on Day 1, but steroids must continue according to the protocol.

Amendment 3: October 18, 2016

1. The opportunity for a subject to undergo one additional re-screen was introduced. This would not include subjects who have failed to meet entry criteria twice as opposed to subjects who have not been able to enter for logistical reasons such as lab results not reported in the screening window.
2. During discussions with the FDA the window in which attacks were assessed was discussed. The protocol therefore specifies a 3-day window for subjects to come into the site and a further 5 days for assessments to be completed. However, the sponsor and the FDA agreed that a wider window will apply for the statistical analysis of the primary endpoint analysis to prevent valid attacks being excluded from the analysis.

Amendment 4: March 8, 2017

1. Text was added that PML has been reported in the setting of B-cell depleting therapies and other immunosuppressive regimens and is a potential risk of treatment with inebilizumab. A subject in Study CD-IAMEDI- 551-1155 developed altered mental state, seizures, and new brain lesions that on brain MRI raised suspicion of PML.
2. Text was changed to a maximum of 252 subjects with NMO/NMOSD will be randomized in a 3:1 ratio to receive IV inebilizumab (300 mg at Day 1 and 300 mg at Day 15) or placebo for a period of 197 days (RCP). Text was added that enrollment of subjects into the study will stop when a total of 67 AC-determined NMOSD attacks occur or when 252 subjects have been randomized, whichever occurs first. For this and all related changes in this amendment, the removal of the interim sample size reassessment resulted from discussion with the FDA regarding the timing of the sample size reassessment as related to the futility analysis. As the study progresses it becomes possible that the futility analysis will occur prior to the sample size reassessment, which would not allow for the performing of the sample size reassessment. Therefore, an agreement was reached with the FDA for the removal of the sample size reassessment from the protocol and increasing the sample size to 252 subjects (or until 67 AC-determined NMOSD attacks have occurred).

3. Added that subjects will be given the option to enter the OLP if they were in the RCP at the time 67 AC-determined attacks had occurred. Text was revised to clarify that subjects who discontinue from the RCP for reasons other than an NMO/NMOSD attack or the occurrence of 67 AC-determined attacks will not be eligible for the OLP.
4. Section 4.8.10.1 (Masked Sample Size Reassessment): This section was removed as the reassessment will not be conducted.

Amendment 5: July 16, 2018

1. Exclusion Criterion 12 was revised to add the stipulation that rituximab treatment with 6 months prior to screening was not exclusionary if a subject has B-cell counts above the LLN.
2. Text was added that low-dose steroid may be permissible if discussed and agreed with the medical monitor, as in some situations low-dose steroid administration will have no impact on the NMO disease course. Also added prohibition of any other immunosuppressant medication (beyond those already named) unless discussed and approved by the medical monitor.
3. Text was added to these sections to clarify that enrollment of subjects into the study will stop when a total of 67 AC-determined NMOSD attacks have occurred or when 252 subjects have been randomized and dosed, whichever occurs first, to account for subjects that are randomized but do not receive investigational product.

Amendment 6: October 11, 2018 (after the last subject had started treatment).

The primary purpose of this amendment was to introduce language related to changes in the study resulting from the Sponsor's decision to accept recommendations from the independent DMC, based on evidence of efficacy and safety, to stop study enrollment and allow subjects in the RCP at that time the option to enter the OLP.

## 6.1.2. Study Results

### Compliance with Good Clinical Practices

The sponsor states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study conduct adhered to the International Council for Harmonization Good Clinical Practice guidelines. The study also adhered to the Good Clinical Practice for Trials on Drug in Japan.

### Financial Disclosure

The sponsor reports that there were 4 investigators who may have received grants for research

that exceeded (b) (6). Only (b) (6) enrolled a significant number of subjects (b) (6). The total number of subjects enrolled by these 4 investigators was 13. If these 4 sites are excluded from the primary analysis, the hazard ratio for the primary endpoint is 0.237 and remains statistically significant ( $p < 0.0001$ ).

### Patient Disposition

Four-hundred and sixty-seven (467) patients signed informed consent and were screened for eligibility. Screen failures were most commonly due to failure to meet one or more inclusion or exclusion criteria (86.4%). Two screened subjects were lost to follow-up and 7 (3%) withdrew consent during the screening period. There was an “other” reason for 23 (9.7%) of the screen failures.

*Reviewer Comment: Most of the “other” reasons for screen failure were related to the eligibility criteria. Several were due to the occurrence of a relapse during the screening period.*

Two-hundred and thirty-one (231) subjects were randomized 3:1 to inebilizumab ( $n = 175$ ) or placebo ( $n = 56$ ). Randomization by country is listed in [Table 2](#).

**Table 2: Number of subjects randomized by country**

| COUNTRY | N Rows |       | INEBILIZUMAB 300mg IV |       | Placebo |       |
|---------|--------|-------|-----------------------|-------|---------|-------|
|         | N      | %     | N                     | %     | N       | %     |
| USA     | 41     | 17.7% | 29                    | 16.6% | 12      | 21.4% |
| RUS     | 23     | 10.0% | 19                    | 10.9% | 4       | 7.1%  |
| POL     | 21     | 9.1%  | 17                    | 9.7%  | 4       | 7.1%  |
| KOR     | 19     | 8.2%  | 16                    | 9.1%  | 3       | 5.4%  |
| COL     | 15     | 6.5%  | 9                     | 5.1%  | 6       | 10.7% |
| PER     | 15     | 6.5%  | 14                    | 8.0%  | 1       | 1.8%  |
| THA     | 11     | 4.8%  | 10                    | 5.7%  | 1       | 1.8%  |
| SRB     | 10     | 4.3%  | 9                     | 5.1%  | 1       | 1.8%  |
| BGR     | 9      | 3.9%  | 7                     | 4.0%  | 2       | 3.6%  |
| DEU     | 9      | 3.9%  | 7                     | 4.0%  | 2       | 3.6%  |
| CZE     | 8      | 3.5%  | 6                     | 3.4%  | 2       | 3.6%  |
| JPN     | 8      | 3.5%  | 7                     | 4.0%  | 1       | 1.8%  |
| MEX     | 8      | 3.5%  | 2                     | 1.1%  | 6       | 10.7% |
| HUN     | 6      | 2.6%  | 4                     | 2.3%  | 2       | 3.6%  |
| ISR     | 5      | 2.2%  | 5                     | 2.9%  | 0       | 0.0%  |
| HKG     | 4      | 1.7%  | 3                     | 1.7%  | 1       | 1.8%  |

| COUNTRY | N Rows |        | INEBILIZUMAB 300mg IV |        | Placebo |        |
|---------|--------|--------|-----------------------|--------|---------|--------|
|         | N      | %      | N                     | %      | N       | %      |
| TUR     | 4      | 1.7%   | 4                     | 2.3%   | 0       | 0.0%   |
| ZAF     | 4      | 1.7%   | 1                     | 0.6%   | 3       | 5.4%   |
| EST     | 3      | 1.3%   | 2                     | 1.1%   | 1       | 1.8%   |
| TWN     | 3      | 1.3%   | 2                     | 1.1%   | 1       | 1.8%   |
| CAN     | 2      | 0.9%   | 2                     | 1.1%   | 0       | 0.0%   |
| AUS     | 1      | 0.4%   | 0                     | 0.0%   | 1       | 1.8%   |
| MDA     | 1      | 0.4%   | 0                     | 0.0%   | 1       | 1.8%   |
| NZL     | 1      | 0.4%   | 0                     | 0.0%   | 1       | 1.8%   |
|         | 231    | 100.0% | 175                   | 100.0% | 56      | 100.0% |

Source: RANDFL\_Y Subset of ADSL TRT01P By (COUNTRY)

All randomized subjects were treated as randomized, with the exception of one subject randomized to inebilizumab who was not treated (subject (b) (6): “Patient was having an NMO attack after randomization but before dosing”). The modified intent to treat population therefore consisted of 174 subjects randomized to inebilizumab and 56 to placebo. Of those subjects who were randomized and treated, ninety-six percent of subjects completed the RCP in both treatment groups. The reasons for discontinuation from the RCP are listed in [Table 3](#).

**Table 3: Disposition of randomized population, ITT**

| Category for Disposition Event | Subcategory for Disposition Event | Standardized Disposition Term | INEBILIZUMAB 300mg IV | Placebo     |
|--------------------------------|-----------------------------------|-------------------------------|-----------------------|-------------|
| DISPOSITION EVENT              | DISCONTINUATION FROM RCP          | COMPLETED                     | 169 (96.6%)           | 54 (96.4%)  |
|                                |                                   | OTHER                         | 3 (1.7%)              | 1 (1.8%)    |
|                                |                                   | ADVERSE EVENT                 | 2 (1.1%)              | 0 (0.0%)    |
|                                |                                   | WITHDRAWAL BY SUBJECT         | 1 (0.6%)              | 1 (1.8%)    |
| Totals                         |                                   | Subjects(filtered)            | 175 (100.0%)          | 56 (100.0%) |
|                                |                                   | 1stCollItemSubjects           | 175 (100.0%)          | 56 (100.0%) |

Source: JRevSelRANDFL\_Y DISPCATbySUBCATbySTDTERMbyTRT01p

The two adverse events that resulted in permanent discontinuation of inebilizumab were “atypical pneumonia” (subject (b) (6)) and “myasthenia gravis” (subject (b) (6)). Two subjects withdrew consent. One subject in the inebilizumab group withdrew consent on day 27; the reason given was “other”; there was an AE of diarrhea on day 15; there had been no relapse events. One subject in the placebo group withdrew consent on day 136; the reason given was “other”; there had been no AEs but there was an evaluation for a possible relapse due to complaints of leg weakness; the event was adjudicated as not a protocol-defined relapse. Of the 4 subjects whose discontinuation term was “other”, one subject randomized to placebo discontinued study procedures but continued in the safety follow-up phase; one subject randomized to inebilizumab was treated but eligibility was not confirmed by the

adjudication committee – this subject was included in the ITT – there were no relapse events; one subject randomized to inebilizumab was discontinued prior to treatment due to an attack; one subject randomized to inebilizumab required corticosteroid treatment for systemic lupus.

One hundred sixty-two subjects treated with inebilizumab and 51 subjects treated with placebo entered the open label treatment phase of the trial.

### Protocol Violations/Deviations

There were 136 “important” protocol deviations in 75 subjects treated with inebilizumab and 65 in 29 subjects treated with placebo ([Table 4](#)).

**Table 4: Important protocol violations/deviations, ITT**

| Deviation Subcategory<br>(DVSCAT)                                                 | Total |       | INEBILIZUMAB<br>300mg IV<br>N=175 |       | Placebo<br>N=56 |        |
|-----------------------------------------------------------------------------------|-------|-------|-----------------------------------|-------|-----------------|--------|
|                                                                                   | N     | %     | N                                 | %     | N               | %      |
| Not in compliance with protocol-required procedure                                | 60    | 26.1% | 41                                | 23.4% | 19              | 33.9%  |
| Other                                                                             | 49    | 21.3% | 26                                | 14.9% | 23              | 41.1%  |
| Received incorrect Investigational Product /dose                                  | 37    | 16.1% | 28                                | 16.0% | 9               | 16.1%  |
| Received prohibited concomitant medication                                        | 31    | 13.5% | 22                                | 12.6% | 9               | 16.1%  |
| Did not fulfill eligibility criteria                                              | 19    | 8.3%  | 14                                | 8.0%  | 5               | 8.9%   |
| Met discontinuation criteria but continued treatment with Investigational Product | 3     | 1.3%  | 3                                 | 1.7%  | 0               | 0.0%   |
| missing                                                                           | 2     | 0.9%  | 2                                 | 1.1%  | 0               | 0.0%   |
| Total                                                                             | 201   | 87.4% | 136                               | 77.7% | 65              | 116.1% |

Source: ADDV TRT01P By (DVSCAT)

*Reviewer Comment: Violations/deviations related to eligibility criteria most often involved B-cell counts that were below the allowable limit; these had the potential to affect safety. “Other” important deviations were more common in the placebo group but, on review of the specific terms, these would not have affected efficacy. Some involved failure to report adverse event that may have affected safety. Many were related to failure to obtain reconsent or use of the incorrect version of the consent form. The same categories of “other” deviations occurred in the inebilizumab group but less frequently. The most common deviations related to protocol-required procedures were related to the process of assessing an attack. This occurred 17 times in the inebilizumab group (9.7% of*

*the treatment group) and 8 times in the placebo group (14.3%). This was most commonly due to failure to complete evaluations within the required time window. Three inebilizumab subjects had a single deviation related to dosing of the investigational product – these all occurred during the OLP. The use of prohibited medications involved the use of corticosteroids in nearly all cases.*

#### Table of Demographic Characteristics

The demographic characteristics of the randomized population are listed in [Table 5](#). The characteristics are adequately balanced by treatment group and typical of a population of patients with NMOSD.

**Table 5: Demographics, ITT population**

| Subgroup                          | Inebilizumab 300mg IV<br>(N = 175)<br>n (%) | Placebo<br>(N = 56)<br>n (%) | Total<br>(N = 231)<br>n (%) |
|-----------------------------------|---------------------------------------------|------------------------------|-----------------------------|
| Sex                               |                                             |                              |                             |
| Female                            | 160 (91.4)                                  | 50 (89.3)                    | 210 (90.9)                  |
| Male                              | 15 (8.6)                                    | 6 (10.7)                     | 21 (9.1)                    |
| Age                               |                                             |                              |                             |
| Mean                              | 42.93                                       | 42.59                        | 42.84                       |
| Standard Deviation                | 11.57                                       | 13.93                        | 12.15                       |
| Minimum                           | 18                                          | 18                           | 18                          |
| Median                            | 43                                          | 42.5                         | 43                          |
| Maximum                           | 73                                          | 74                           | 74                          |
| Age Group                         |                                             |                              |                             |
| Age Group 1 (AGE < 40)            | 68 (38.9)                                   | 25 (44.6)                    | 93 (40.3)                   |
| Age Group 2 (40 <= AGE)           | 107 (61.1)                                  | 31 (55.4)                    | 138 (59.7)                  |
| Race                              |                                             |                              |                             |
| American Indian or Alaskan Native | 14 (8.0)                                    | 5 (8.9)                      | 19 (8.2)                    |
| Asian                             | 39 (22.3)                                   | 8 (14.3)                     | 47 (20.3)                   |
| Black or African American         | 15 (8.6)                                    | 5 (8.9)                      | 20 (8.7)                    |
| Multiple Categories Checked       | 1 (0.6)                                     | 0 (0.0)                      | 1 (0.4)                     |
| Other                             | 14 (8.0)                                    | 10 (17.9)                    | 24 (10.4)                   |
| White                             | 92 (52.6)                                   | 28 (50.0)                    | 120 (51.9)                  |
| Ethnicity                         |                                             |                              |                             |
| Hispanic or Latino                | 28 (16.0)                                   | 15 (26.8)                    | 43 (18.6)                   |

| Subgroup               | Inebilizumab 300mg IV<br>(N = 175)<br>n (%) | Placebo<br>(N = 56)<br>n (%) | Total<br>(N = 231)<br>n (%) |
|------------------------|---------------------------------------------|------------------------------|-----------------------------|
| Not Hispanic or Latino | 147 (84.0)                                  | 41 (73.2)                    | 188 (81.4)                  |
| Region                 |                                             |                              |                             |
| Africa                 | 1 (0.6)                                     | 3 (5.4)                      | 4 (1.7)                     |
| Asia                   | 47 (26.9)                                   | 7 (12.5)                     | 54 (23.4)                   |
| Canada                 | 2 (1.1)                                     | 0 (0.0)                      | 2 (0.9)                     |
| Europe                 | 71 (40.6)                                   | 19 (33.9)                    | 90 (39.0)                   |
| Other                  | 0 (0.0)                                     | 2 (3.6)                      | 2 (0.9)                     |
| South America          | 25 (14.3)                                   | 13 (23.2)                    | 38 (16.5)                   |
| United States          | 29 (16.6)                                   | 12 (21.4)                    | 41 (17.7)                   |

Source: OCS DEM TOOL custom age groups

*Reviewer Comment: The demographic characteristics of the population studied do not pose any obvious limitations to translation of results to the US population. The population in the table above is the full ITT which includes one subject in the inebilizumab group who was not treated. The demographics for the modified ITT, including only subjects with at least one dose of investigational treatment, do not differ significantly.*

The demographic characteristics of the population seropositive for anti-AQP4 IgG ([Table 6](#)) do not appear to differ significantly from the full ITT population.

**Table 6: Demographics of the AQP4 IgG seropositive subpopulation of the ITT**

| Subgroup           | MEDI-551 300mg IV<br>(N = 161)<br>n (%) | Placebo<br>(N = 52)<br>n (%) | Total<br>(N = 213)<br>n (%) |
|--------------------|-----------------------------------------|------------------------------|-----------------------------|
| Sex                |                                         |                              |                             |
| Female             | 151 (93.8)                              | 49 (94.2)                    | 200 (93.9)                  |
| Male               | 10 (6.2)                                | 3 (5.8)                      | 13 (6.1)                    |
| Age                |                                         |                              |                             |
| Mean               | 43.17                                   | 42.42                        | 42.99                       |
| Standard Deviation | 11.59                                   | 14.33                        | 12.29                       |
| Minimum            | 18                                      | 18                           | 18                          |
| Median             | 43                                      | 43                           | 43                          |
| Maximum            | 73                                      | 74                           | 74                          |

| Subgroup                          | MEDI-551 300mg IV<br>(N = 161)<br>n (%) | Placebo<br>(N = 52)<br>n (%) | Total<br>(N = 213)<br>n (%) |
|-----------------------------------|-----------------------------------------|------------------------------|-----------------------------|
| Age Group                         |                                         |                              |                             |
| Age Group 1 (AGE < 40)            | 61 (37.9)                               | 24 (46.2)                    | 85 (39.9)                   |
| Age Group 2 (40 <= AGE)           | 100 (62.1)                              | 28 (53.8)                    | 128 (60.1)                  |
| Race                              |                                         |                              |                             |
| American Indian or Alaskan Native | 11 (6.8)                                | 5 (9.6)                      | 16 (7.5)                    |
| Asian                             | 37 (23.0)                               | 8 (15.4)                     | 45 (21.1)                   |
| Black or African American         | 14 (8.7)                                | 5 (9.6)                      | 19 (8.9)                    |
| Multiple Categories Checked       | 1 (0.6)                                 | 0 (0.0)                      | 1 (0.5)                     |
| Other                             | 12 (7.5)                                | 10 (19.2)                    | 22 (10.3)                   |
| White                             | 86 (53.4)                               | 24 (46.2)                    | 110 (51.6)                  |
| Ethnicity                         |                                         |                              |                             |
| Hispanic or Latino                | 25 (15.5)                               | 15 (28.8)                    | 40 (18.8)                   |
| Not Hispanic or Latino            | 136 (84.5)                              | 37 (71.2)                    | 173 (81.2)                  |
| Region                            |                                         |                              |                             |
| Africa                            | 1 (0.6)                                 | 3 (5.8)                      | 4 (1.9)                     |
| Asia                              | 43 (26.7)                               | 7 (13.5)                     | 50 (23.5)                   |
| Canada                            | 2 (1.2)                                 | 0 (0.0)                      | 2 (0.9)                     |
| Europe                            | 66 (41.0)                               | 16 (30.8)                    | 82 (38.5)                   |
| Other                             | 0 (0.0)                                 | 2 (3.8)                      | 2 (0.9)                     |
| South America                     | 22 (13.7)                               | 13 (25.0)                    | 35 (16.4)                   |
| United States                     | 27 (16.8)                               | 11 (21.2)                    | 38 (17.8)                   |

Source: LDR2020-01-28\_DEMTOOL\_ASTRFL\_Y\_AQP4pos

#### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Over 90% of subjects were positive for the anti-AQP4 IgG antibody at the time of randomization. The baseline level of disability was moderate as reflected by a baseline EDSS of approximately 4 (fully ambulatory without aid, up and about 12 hours per day despite relatively severe disability; able to walk without aid 500 meters) and a baseline modified Rankin Scale (mRS) score of approximately 2 (Ambulatory; able to look after own affairs; unable to carry out some previous activities). Most previous attacks had been either optic neuritis or myelitis with less frequent attacks involving the brainstem ([Table 7](#)).

*Reviewer Comment: Although the protocol indicated that the anti-AQP4 IgG antibody status would be determined using a "commercially available visual*

fluorescence-observation cell binding assay (EUROIMMUN)", the CSR states that "AQP4-IgG serostatus was determined at screening by testing conducted by a central laboratory (b) (4) using a modified commercially available visual fluorescence-observation cell-binding assay (EUROIMMUN)". In response to an Additional Information Request, the sponsor confirmed that the (b) (4) modification of the EUROIMMUN method was used to qualify subjects and that the device is not cleared by CDRH. Quantitative AQP4-IgG titers were also conducted by a central laboratory using a flow cytometry method. The specific method is not provided, and the CSR indicates that the quantitative results collected during treatment will be reported later.

**Table 7: Baseline NMOSD characteristics**

|                                         | MEDI-551 300mg IV<br>N=174 |       | Placebo<br>N=56 |       |
|-----------------------------------------|----------------------------|-------|-----------------|-------|
|                                         | N                          | %     | N               | %     |
| AQP4 IgG                                |                            |       |                 |       |
| Analysis value (ADSL dataset)           |                            |       |                 |       |
| seronegative                            | 14                         | 8.0%  | 4               | 7.1%  |
| seropositive                            | 161                        | 92%   | 52              | 92.9% |
| EDSS                                    |                            |       |                 |       |
| Mean ± SD                               | 3.81±1.81                  |       | 4.19±1.68       |       |
| Median                                  | 3.5                        |       | 4               |       |
| Range                                   | 0-8                        |       | 1-8             |       |
| mRS                                     |                            |       |                 |       |
| Mean ± SD                               | 1.81±1.3                   |       | 2.07±1.26       |       |
| Median                                  | 2                          |       | 2               |       |
| Range                                   | 0-5                        |       | 0-5             |       |
| Disease duration                        |                            |       |                 |       |
| <5 years                                | 144                        | 82.8% | 46              | 82.1% |
| ≥5 years                                | 30                         | 17.2% | 10              | 17.9% |
| Mean ± SD, yrs                          | 2.41±3.3                   |       | 2.77±3.5        |       |
| Median, yrs                             | 1.06                       |       | 1.38            |       |
| Range, yrs                              | 0.07-22.2                  |       | 0.19-16.9       |       |
| First attack                            |                            |       |                 |       |
| Brain/Brainstem                         | 9                          | 5.2%  | 9               | 16.1% |
| Brain/Brainstem Myelitis                | 5                          | 2.9%  | 0               | 0.0%  |
| Brain/Brainstem Myelitis Optic neuritis | 2                          | 1.1%  | 4               | 7.1%  |
| Brain/Brainstem Optic neuritis          | 1                          | 0.6%  | 0               | 0.0%  |
| Myelitis                                | 72                         | 41.4% | 20              | 35.7% |
| Myelitis Optic neuritis                 | 14                         | 8.0%  | 4               | 7.1%  |

|                                         | MEDI-551 300mg IV<br>N=174 |       | Placebo<br>N=56 |       |
|-----------------------------------------|----------------------------|-------|-----------------|-------|
|                                         | N                          | %     | N               | %     |
| Optic neuritis                          | 71                         | 40.8% | 19              | 33.9% |
| Number of prior relapses                |                            |       |                 |       |
| 1                                       | 25                         | 14.4% | 14              | 25.0% |
| 2                                       | 39                         | 22.4% | 11              | 19.6% |
| 3                                       | 29                         | 16.7% | 6               | 10.7% |
| 4                                       | 21                         | 12.1% | 8               | 14.3% |
| 5                                       | 16                         | 9.2%  | 4               | 7.1%  |
| 6                                       | 15                         | 8.6%  | 2               | 3.6%  |
| 7                                       | 8                          | 4.6%  | 4               | 7.1%  |
| 8                                       | 7                          | 4.0%  | 1               | 1.8%  |
| 9                                       | 1                          | 0.6%  | 1               | 1.8%  |
| 10                                      | 3                          | 1.7%  | 2               | 3.6%  |
| >10                                     | 9                          | 5.2%  | 3               | 5.4%  |
| Number of prior myelitis relapses       |                            |       |                 |       |
| Number with any                         | 143                        |       | 44              |       |
| Mean ± SD                               | 3.38±3.39                  |       | 3.45±4.25       |       |
| Median                                  | 2                          |       | 2               |       |
| Range                                   | 2-20                       |       | 2-26            |       |
| None                                    | 31 (17.8%)                 |       | 12 (21.4%)      |       |
| Number of prior optic neuritis relapses |                            |       |                 |       |
| Number with any                         | 135 (77.6%)                |       | 39 (69.6)       |       |
| Mean ± SD                               | 2.35±1.99                  |       | 2.31±1.99       |       |
| Median                                  | 2                          |       | 2               |       |
| Range                                   | 1-16                       |       | 1-9             |       |
| None                                    | 39 (22.4%)                 |       | 17 (30.4%)      |       |
| Previous brainstem/brain relapses       |                            |       |                 |       |
| Number with any                         | 34                         |       | 19              |       |
| Mean ± SD                               | 1.5±1.05                   |       | 1.7±0.95        |       |
| Median                                  | 1                          |       | 1               |       |
| Range                                   | 1-6                        |       | 1-4             |       |
| None                                    | 140                        |       | 37              |       |

Source: Reviewer table taken from ADMH and ADSL databases

*Reviewer Comment: The AQP4-IgG serostatus was based on the result from the central laboratory at the time of screening, which took precedence over any previous results. Eighteen randomized subjects were seronegative. One of these (b) (6) was not treated and excluded from the mITT (listed as the ITT by the sponsor). The remaining 17 were reviewed by the Seronegative Eligibility Committee. The sponsor provides a dossier for each of these subjects that include more than adequate documentation of the clinical and MRI information reviewed in the process for determining the eligibility of these subjects. Further analysis of the characteristics of study subjects by AQP4-IgG status follows.*

### Anti-AQP4-IgG status

The 17 subjects who were randomized and treated and who were seronegative for the anti-AQP4-IgG antibody did not appear to differ significantly from those who were seropositive. The baseline EDSS score was somewhat higher in the seropositive group ([Table 8](#)). The median baseline mRS was 2 for both groups. Measures of previous disease activity such as the number of previous relapses ([Table 9](#)), time since the most recent relapse, time since the first relapse, and type of the first relapse show no major differences when the seronegative and seropositive populations are compared. There does not appear to any major differences in previous NMOSD therapy ([Table 10](#)).

*Reviewer Comment: The number of seronegative subjects in the mITT is small compared to the seropositive population. Therefore, comparison of disease characteristics is limited at best.*

**Table 8: Baseline EDSS score by strata, mITT**

| STRATA                        | Baseline EDSS (AVAL) |      |         |     |     |        |
|-------------------------------|----------------------|------|---------|-----|-----|--------|
|                               | Total                | Mean | Std Dev | Min | Max | Median |
| AQP4-IgG seronegative – N=17  | 17                   | 3.44 | 2.16    | 0   | 7.5 | 3.5    |
| AQP4-IgG seropositive – N=213 | 213                  | 3.94 | 1.75    | 0   | 8   | 3.5    |

Source: ABLFL\_Y Subset of PARAM\_EDSS Subset of ADQSED AVAL By (STRATA).jmp

**Table 9: Number of relapses prior to randomization, by baseline AQP4-IgG status, mITT**

| MH5CAT | Total<br>N=230 |    | Seronegative<br>N=17 |      | Seropositive<br>N=213 |      |
|--------|----------------|----|----------------------|------|-----------------------|------|
|        | N*             | %  | N*                   | %    | N*                    | %    |
| <2     | 39             | 17 | 2                    | 11.8 | 37                    | 17.4 |
| >=2    | 191            | 83 | 15                   | 88.2 | 176                   | 82.6 |

Source: MHCAT\_DISEASEHX Subset of ADMH By (USUBJID, STRATA, MH5CAT) NUSUBJIDbySTRATA By (MH5CAT).jmp

\*: N = NUSUBJID

**Table 10: Previous NMOSD maintenance therapy, by AQP4 baseline status**

| Previous maintenance therapy | Seropositive<br>N=213 | Seronegative<br>N=17 |
|------------------------------|-----------------------|----------------------|
|                              | N, %                  | N, %                 |
| Monoclonal antibodies        | 16, 7.5%              | 1, 5.9%              |
| Selective immunosuppressants | 33, 15.5%             | 1, 5.9%              |
| Other immunosuppressants     | 83, 39%               | 3, 17.7%             |
| Any disease modifying drug*  | 115, 54%              | 5, 29.4%             |

**Source:** CMCLAS\_selected group Subset of CMSCAT\_MAINTENANCE Subset of CMCAT\_NMOMEDHX Subset of ITTFL\_Y Subset of ADCM By (USUBJID, STRATA) NUSUBJID By (STRATA).jmp

\*: Includes Interferons, monoclonal antibodies, nitrogen mustard analogues, other immunosuppressants, other immunostimulants, selective immunosuppressants

### Concomitant Medications

The most common medications related to treatment of NMOSD prior to randomization are listed by Medication Class in [Table 11](#) and by Standard Medication Name in [Table 12](#). Nearly all subjects in both treatment groups had been treated with immunosuppressants and corticosteroids in the past. There are no major differences between the treatment groups in the use of these therapies.

**Table 11: Prior NMOSD Treatment, Medication Class, mITT**

| Medication Class                               | INEBILIZUMAB 300mg IV<br>N=174 | Placebo<br>N=56 |
|------------------------------------------------|--------------------------------|-----------------|
| GLUCOCORTICOIDS                                | 167 (96.0%)                    | 52 (92.9%)      |
| OTHER IMMUNOSUPPRESSANTS                       | 66 (37.9%)                     | 22 (39.3%)      |
| SELECTIVE IMMUNOSUPPRESSANTS                   | 28 (16.1%)                     | 7 (12.5%)       |
| MONOCLONAL ANTIBODIES                          | 13 (7.5%)                      | 5 (8.9%)        |
| INTERFERONS                                    | 8 (4.6%)                       | 2 (3.6%)        |
| IMMUNOGLOBULINS, NORMAL HUMAN                  | 6 (3.4%)                       | 3 (5.4%)        |
| NITROGEN MUSTARD ANALOGUES                     | 4 (2.3%)                       | 2 (3.6%)        |
| CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS | 4 (2.3%)                       | 1 (1.8%)        |
| ANTHRACYCLINES AND RELATED SUBSTANCES          | 4 (2.3%)                       | 0 (0.0%)        |
| CALCINEURIN INHIBITORS                         | 2 (1.1%)                       | 1 (1.8%)        |
| Subjects(filtered)                             | 172 (98.9%)                    | 54 (96.4%)      |
| 1stCollItemSubjects Treated                    | 174 (100.0%)                   | 56 (100.0%)     |

**Source:** JRevSelASTRFL\_Y CMCLASbyADSLTRT01PfiltCMCAT\_NMOMEDHX

**Table 12: Prior NMOSD Treatment, Standard Medication Name, 10 most common, mITT**

| Standardized Medication Name        | INEBILIZUMAB 300mg IV<br>N=174 | Placebo<br>N=56 |
|-------------------------------------|--------------------------------|-----------------|
| METHYLPREDNISOLONE                  | 115 (66.1%)                    | 36 (64.3%)      |
| AZATHIOPRINE                        | 64 (36.8%)                     | 22 (39.3%)      |
| METHYLPREDNISOLONE SODIUM SUCCINATE | 49 (28.2%)                     | 18 (32.1%)      |
| PREDNISOLONE                        | 50 (28.7%)                     | 9 (16.1%)       |
| PREDNISONE                          | 43 (24.7%)                     | 11 (19.6%)      |
| MYCOPHENOLATE MOFETIL               | 27 (15.5%)                     | 7 (12.5%)       |
| RITUXIMAB                           | 13 (7.5%)                      | 4 (7.1%)        |
| DEXAMETHASONE                       | 12 (6.9%)                      | 3 (5.4%)        |
| IMMUNOGLOBULIN HUMAN NORMAL         | 5 (2.9%)                       | 3 (5.4%)        |
| INTERFERON BETA-1A                  | 6 (3.4%)                       | 1 (1.8%)        |

| Standardized Medication Name | INEBILIZUMAB 300mg IV<br>N=174 | Placebo<br>N=56 |
|------------------------------|--------------------------------|-----------------|
| Subjects(filtered)           | 172 (98.9%)                    | 54 (96.4%)      |
| 1stCollItemSubjects Treated  | 174 (100.0%)                   | 56 (100.0%)     |

Source: JRevSelASTRFL\_Y CMDECODbyADSLTRT01PfiltCMCAT\_NMOMEDHX

### Comorbidities

The most common comorbid conditions are listed in [Table 13](#). These conditions were specified in the case report form as conditions of interest that were known to occur with increased frequency in patients with NMOSD<sup>23</sup>.

**Table 13: Comorbid conditions**

| MHTERM                                                 | MEDI-551 300mg IV<br>N=174 |       | Placebo<br>N=56 |       |
|--------------------------------------------------------|----------------------------|-------|-----------------|-------|
|                                                        | N                          | %     | N               | %     |
| Autoimmune thyroiditis                                 | 7                          | 4.0%  | 1               | 1.8%  |
| Celiac disease                                         | 1                          | 0.6%  | 0               | 0.0%  |
| Insulin dependent diabetes mellitus (IDDM)             | 0                          | 0.0%  | 1               | 1.8%  |
| Myasthenia gravis                                      | 5                          | 2.9%  | 1               | 1.8%  |
| Other                                                  | 6                          | 3.4%  | 4               | 7.1%  |
| Pernicious anaemia                                     | 2                          | 1.1%  | 0               | 0.0%  |
| Rheumatoid arthritis                                   | 3                          | 1.7%  | 0               | 0.0%  |
| Sjögren's syndrome                                     | 5                          | 2.9%  | 2               | 3.6%  |
| Systemic lupus erythematosus                           | 3                          | 1.7%  | 0               | 0.0%  |
| Percent of treatment group with any comorbid condition | 32                         | 18.4% | 9               | 16.1% |
| Total population randomized                            | 175                        | 100%  | 56              | 100%  |

Source: MHCAT\_COMORBID Subset of ADMH By (USUBJID, TRT01P, MHTERM) NSUBJID TRT01P By (MHTERM).jmp

The most common conditions by medical history system class are listed in [Table 14](#) and by standard medical history term in [Table 15](#).

**Table 14: Medical history, by body system, 20% or more of either treatment group**

| MHBODSYS                                        | MEDI-551 300mg IV<br>N=174 |       | Placebo<br>N=56 |       |
|-------------------------------------------------|----------------------------|-------|-----------------|-------|
|                                                 | N                          | %     | N               | %     |
| Gastrointestinal disorders                      | 43                         | 24.7% | 21              | 37.5% |
| Musculoskeletal and connective tissue disorders | 34                         | 19.5% | 17              | 30.4% |
| Nervous system disorders                        | 37                         | 21.3% | 14              | 25.0% |
| Psychiatric disorders                           | 35                         | 20.1% | 15              | 26.8% |
| Infections and infestations                     | 29                         | 16.7% | 19              | 33.9% |
| Surgical and medical procedures                 | 39                         | 22.4% | 8               | 14.3% |
| Vascular disorders                              | 30                         | 17.2% | 11              | 19.6% |

| MHBODSYS                           | MEDI-551 300mg IV<br>N=174 |       | Placebo<br>N=56 |       |
|------------------------------------|----------------------------|-------|-----------------|-------|
|                                    | N                          | %     | N               | %     |
| Metabolism and nutrition disorders | 25                         | 14.4% | 13              | 23.2% |

Source: MHCAT\_GENMEDHX Subset of ADMH By (USUBJID, TRT01P, MHBODSYS) MHSOCbyTRT01P By (MHBODSYS)

**Table 15: Medical history standardized terms, 5% or more of either treatment group**

| MHDECOD                 | MEDI-551 300mg IV |       | Placebo |       |
|-------------------------|-------------------|-------|---------|-------|
|                         | N                 | %     | N       | %     |
| Hypertension            | 21                | 12.1% | 11      | 19.6% |
| Constipation            | 19                | 10.9% | 12      | 21.4% |
| Depression              | 15                | 8.6%  | 4       | 7.1%  |
| Insomnia                | 11                | 6.3%  | 5       | 8.9%  |
| Headache                | 10                | 5.7%  | 5       | 8.9%  |
| Hypothyroidism          | 9                 | 5.2%  | 4       | 7.1%  |
| Urinary tract infection | 5                 | 2.9%  | 8       | 14.3% |
| Back pain               | 10                | 5.7%  | 2       | 3.6%  |

Source: MHCAT\_GENMEDHX Subset of ADMH By (USUBJID, TRT01P, MHDECOD) NUSUBJIDbyTRT01P By (MHDECOD).jmp

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

### Concomitant Medications during the RCP

The most common concomitant medications during the RCP are shown by Medication Class in [Table 16](#) and by Standard Medication Name in [Table 17](#). A relatively small proportion of subjects continued on a low dose of corticosteroids during the RCP. A dose of no more than 20 mg per day was allowed by protocol.

**Table 16: Concomitant Medications during the RCP, Medication Class, most common, mITT**

| Medication Class                        | INEBILIZUMAB 300mg IV | Placebo     |
|-----------------------------------------|-----------------------|-------------|
| OTHER ANALGESICS AND ANTIPYRETICS       | 69 (39.7%)            | 29 (51.8%)  |
| PROTON PUMP INHIBITORS                  | 62 (35.6%)            | 28 (50.0%)  |
| ANILIDES                                | 60 (34.5%)            | 23 (41.1%)  |
| OTHER CENTRALLY ACTING AGENTS           | 39 (22.4%)            | 19 (33.9%)  |
| PROPIONIC ACID DERIVATIVES              | 44 (25.3%)            | 14 (25.0%)  |
| FLUOROQUINOLONES                        | 30 (17.2%)            | 18 (32.1%)  |
| VITAMIN D AND ANALOGUES                 | 30 (17.2%)            | 16 (28.6%)  |
| BENZODIAZEPINE DERIVATIVES              | 26 (14.9%)            | 17 (30.4%)  |
| H2-RECEPTOR ANTAGONISTS                 | 24 (13.8%)            | 10 (17.9%)  |
| SELECTIVE SEROTONIN REUPTAKE INHIBITORS | 24 (13.8%)            | 8 (14.3%)   |
| GLUCOCORTICOIDS                         | 22 (12.6%)            | 9 (16.1%)   |
| Subjects(filtered)                      | 160 (92.0%)           | 55 (98.2%)  |
| 1stCollItemSubjects                     | 174 (100.0%)          | 56 (100.0%) |

Source: JRevSelASTRFL\_Y CMCLASbyTRT01PfiltCMCAT\_CONMED

**Table 17: Concomitant Medications during the RCP, Standard Medication Name, most common, ITT**

| Standardized Medication Name | INEBILIZUMAB 300mg IV | Placebo    |
|------------------------------|-----------------------|------------|
| PARACETAMOL                  | 51 (29.3%)            | 20 (35.7%) |
| GABAPENTIN                   | 37 (21.3%)            | 14 (25.0%) |
| BACLOFEN                     | 25 (14.4%)            | 18 (32.1%) |
| CARBAMAZEPINE                | 27 (15.5%)            | 11 (19.6%) |
| IBUPROFEN                    | 28 (16.1%)            | 9 (16.1%)  |
| PREGABALIN                   | 24 (13.8%)            | 13 (23.2%) |
| CIPROFLOXACIN                | 21 (12.1%)            | 12 (21.4%) |
| OMEPRazole                   | 22 (12.6%)            | 10 (17.9%) |
| PANTOPRAZOLE                 | 15 (8.6%)             | 8 (14.3%)  |
| COLECALCIFEROL               | 13 (7.5%)             | 9 (16.1%)  |

Source: JRevSelASTRFL\_Y CMDECODbyTRT01PfiltCMCAT\_CONMED

### Efficacy Results – Primary Endpoint

There were 64 acute attacks adjudicated by the Adjudication Committee (AC), 36 in the group treated with inebilizumab (20.7% of the treatment group) and 28 in the placebo group (50% of the treatment group). Twenty-one of the 36 (58.3%) in the inebilizumab group were confirmed and 22 of the 28 (79%) in the placebo group were confirmed.

*Reviewer Comment: The reasons for the higher confirmation rate in the placebo group are unclear. The mean change in EDSS at attack visits is not different*

*between the two treatment groups (Table 18) or when compared by incremental category of change (Table 19). The mean change of 1 point supports that these were clinically relevant attacks.*

**Table 18: Mean change in EDSS from baseline at attack visits**

| TRT01P            | EDSS change from baseline at attack visit (CHG) |      |         |      |     |        |           |
|-------------------|-------------------------------------------------|------|---------|------|-----|--------|-----------|
|                   | N                                               | Mean | Std Dev | Min  | Max | Median | N Missing |
| MEDI-551 300mg IV | 35                                              | 1.13 | 1.26    | -0.5 | 4.5 | 1      | 0         |
| Placebo           | 28                                              | 1.07 | 1.31    | -0.5 | 4.5 | 1      | 0         |

Source: VISIT\_ATTACK Subset of EPOCH\_RCT Subset of PARAM\_EDSS Subset of ADQSED CHG By (TRT01P).jmp

There was relatively little difference in the change from baseline at the attack visit categorized in increments of one.

**Table 19: Incremental change in EDSS from baseline at attack visits**

| Change category | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|-----------------|-------|--------|-------------------|--------|---------|--------|
|                 | N     | %      | N                 | %      | N       | %      |
| <0              | 4     | 6.3%   | 2                 | 5.7%   | 2       | 7.1%   |
| >0 to 1         | 24    | 38.1%  | 14                | 40.0%  | 10      | 35.7%  |
| >1 to 2         | 7     | 11.1%  | 4                 | 11.4%  | 3       | 10.7%  |
| >2 to 3         | 6     | 9.5%   | 4                 | 11.4%  | 2       | 7.1%   |
| >3 to 4         | 4     | 6.3%   | 2                 | 5.7%   | 2       | 7.1%   |
| >4 to 5         | 18    | 28.6%  | 9                 | 25.7%  | 9       | 32.1%  |
| Total           | 63    | 100.0% | 35                | 100.0% | 28      | 100.0% |

Source: VISIT\_ATTACK Subset of EPOCH\_RCT Subset of PARAM\_EDSS Subset of ADQSED TRT01P By (Change category).jmp

The proportion of subjects meeting one or more of the criteria that were used to determine an AC-confirmed attack did not vary greatly by treatment group (Table 20). Slightly more subjects treated with inebilizumab met criterion 12, an attack of myelitis with a 2-point increase on one or more relevant FSS compared to last visit). More subjects treated with placebo met criterion 1 (greater than 15-character drop in high-contrast Landolt C Broken Rings chart from last visit). See Appendix 13.3 for the attack criteria.

**Table 20: Criteria met for adjudication of attacks**

| PARAM                              | Total |       | MEDI-551 300mg IV |       | Placebo |       |
|------------------------------------|-------|-------|-------------------|-------|---------|-------|
|                                    | N     | %     | N                 | %     | N       | %     |
| AC reported Criterion 12 - overall | 21    | 26.6% | 11                | 32.4% | 10      | 22.2% |
| AC reported Criterion 1 - overall  | 11    | 13.9% | 4                 | 11.8% | 7       | 15.6% |
| AC reported Criterion 13 - overall | 8     | 10.1% | 2                 | 5.9%  | 6       | 13.3% |
| AC reported Criterion 14 - overall | 8     | 10.1% | 3                 | 8.8%  | 5       | 11.1% |

| PARAM                              | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|------------------------------------|-------|--------|-------------------|--------|---------|--------|
|                                    | N     | %      | N                 | %      | N       | %      |
| AC reported Criterion 2 - overall  | 5     | 6.3%   | 1                 | 2.9%   | 4       | 8.9%   |
| AC reported Criterion 5 - overall  | 5     | 6.3%   | 3                 | 8.8%   | 2       | 4.4%   |
| AC reported Criterion 10 - overall | 4     | 5.1%   | 2                 | 5.9%   | 2       | 4.4%   |
| AC reported Criterion 15 - overall | 3     | 3.8%   | 1                 | 2.9%   | 2       | 4.4%   |
| AC reported Criterion 6 - overall  | 3     | 3.8%   | 2                 | 5.9%   | 1       | 2.2%   |
| AC reported Criterion 9 - overall  | 3     | 3.8%   | 2                 | 5.9%   | 1       | 2.2%   |
| AC reported Criterion 16 - overall | 2     | 2.5%   | 0                 | 0.0%   | 2       | 4.4%   |
| AC reported Criterion 8 - overall  | 2     | 2.5%   | 0                 | 0.0%   | 2       | 4.4%   |
| AC reported Criterion 11 - overall | 1     | 1.3%   | 1                 | 2.9%   | 0       | 0.0%   |
| AC reported Criterion 3 - overall  | 1     | 1.3%   | 1                 | 2.9%   | 0       | 0.0%   |
| AC reported Criterion 4 - overall  | 1     | 1.3%   | 1                 | 2.9%   | 0       | 0.0%   |
| AC reported Criterion 7 - overall  | 1     | 1.3%   | 0                 | 0.0%   | 1       | 2.2%   |
|                                    | 79    | 100.0% | 34                | 100.0% | 45      | 100.0% |

Source: PARAM\_CRITERIA OVERALL Subset of ADZJ TRT01P By (PARAM)

Fifty-one subjects met one or more of the criteria for an AC-confirmed attack. The proportion attacks that were determined to meet criteria for optic neuritis, myelitis or a brainstem attack was similar between the two treatment groups (the proportion meeting criteria for the full treatment group was, of course, higher for the placebo group, consistent with the overall difference in relapse rate).

**Table 21: Proportion of attacks meeting criteria, by total attacks and by treatment group**

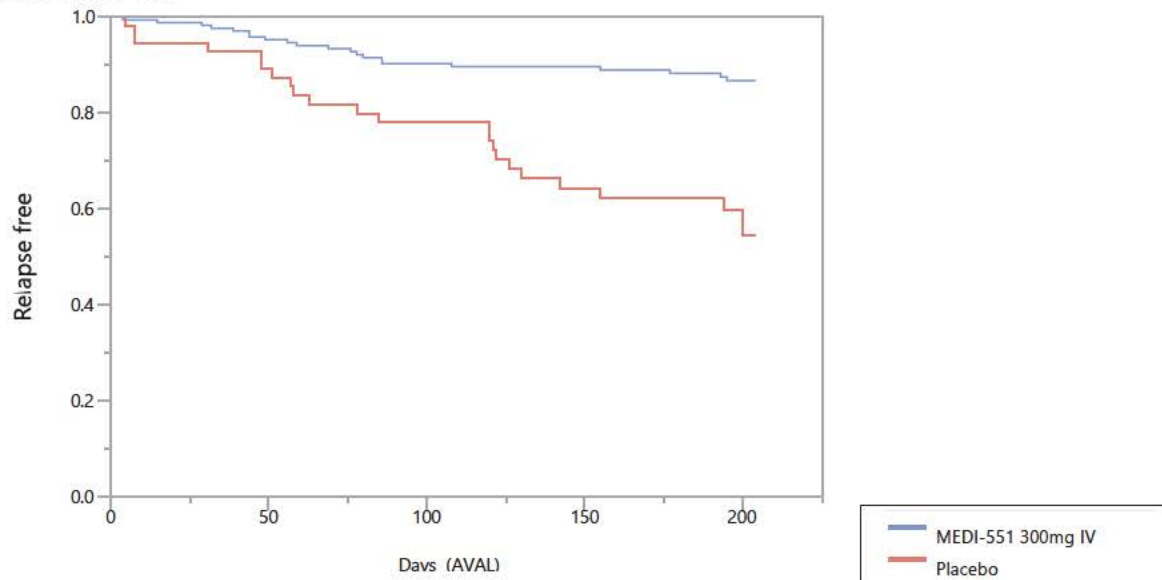
| AVALCAT1       | MEDI-551 300mg IV |                      |              | Placebo    |                      |              |
|----------------|-------------------|----------------------|--------------|------------|----------------------|--------------|
|                | N(USUBJID)        | % of treatment group | % of attacks | N(USUBJID) | % of treatment group | % of attacks |
| Brainstem      | 0                 | 0.0%                 | 0.0%         | 2          | 3.6%                 | 7.1%         |
| Myelitis       | 13                | 7.5%                 | 56.5%        | 15         | 26.8%                | 53.6%        |
| Optic neuritis | 10                | 5.7%                 | 43.5%        | 11         | 19.6%                | 39.3%        |
| Total          | 23                |                      |              | 28         |                      |              |

PARCAT1\_Criteria by AC overall Subset of ADZJ By (USUBJID, TRT01P, AVALCAT1) NSUBJID by TRT01P By (AVALCAT1)

The primary measure of efficacy was the time (days) from Day 1 to the onset of an AC-determined NMOSD attack on or before the end of RCP (Day 197/discontinuation visit). Analyzed using the Kaplan-Meier model, treatment with inebilizumab was significantly superior to placebo for the primary analysis (**Figure 1**,  $p < 0.0001$ , log-rank test). The unadjusted odds ratio was 0.212 (reviewer analysis). Using the Cox regression model, the sponsor reports a hazard ratio of 0.272 (95% CI: 0.1496, 0.4961).

**Figure 1: Time to first AC-confirmed attack, mITT**

**Product-Limit Survival Fit  
Survival Plot**



Time to event: AVAL  
Censored by: CNSR  
Censor Code: 1  
Grouped by: TRT01P

| Group             | Number failed | Number censored |
|-------------------|---------------|-----------------|
| MEDI-551 300mg IV | 21            | 153             |
| Placebo           | 22            | 34              |
| Combined          | 43            | 187             |

| Tests Between Groups |           |    |            |
|----------------------|-----------|----|------------|
| Test                 | ChiSquare | DF | Prob>ChiSq |
| Log-Rank             | 20.7000   | 1  | <.0001*    |
| Wilcoxon             | 18.1311   | 1  | <.0001*    |

Source: TTFE TTAA by TRT01P.jrp

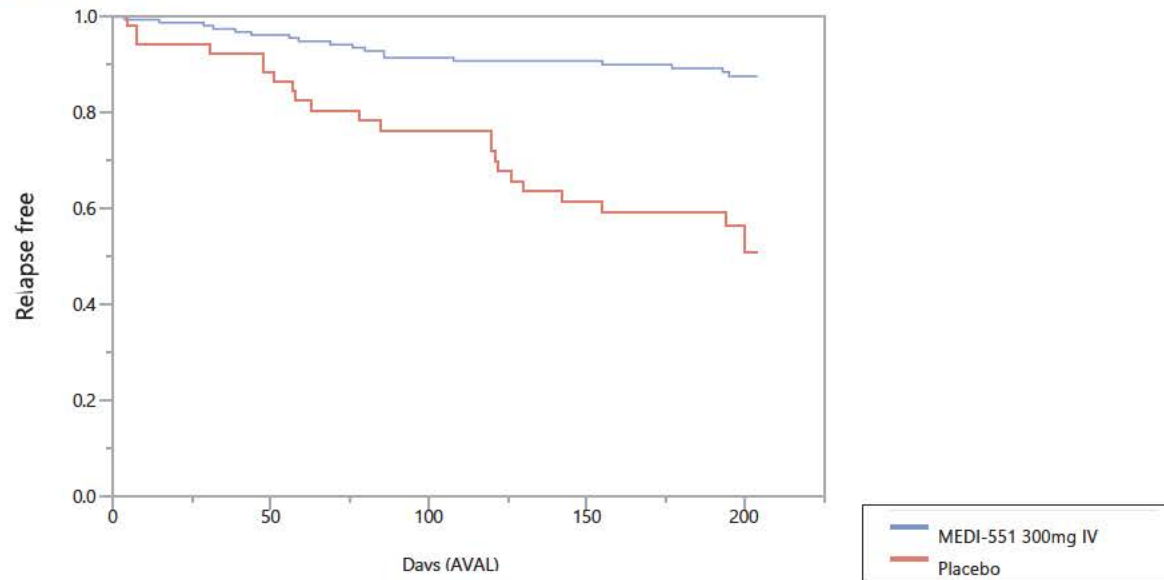
**Primary Endpoint by AQP4-IgG status**

For the 213 subject who were AQP4-IgG positive, the time to AC-confirmed relapse is shown in [Figure 2](#) and for those who were negative in [Figure 3](#). Although there were relatively few seronegative subjects, none of 4 placebo subjects had a relapse compared to 3 of 13 subjects treated with inebilizumab.

**Figure 2: Time to first AC-confirmed relapse, AQP4-IgG positive subjects**

**Product-Limit Survival Fit STRATA=AQP4-IgG seropositive**

**Survival Plot**



**Summary**

| Group             | Number failed | Number censored |
|-------------------|---------------|-----------------|
| MEDI-551 300mg IV | 18            | 143             |
| Placebo           | 22            | 30              |
| Combined          | 40            | 173             |

**Tests Between Groups**

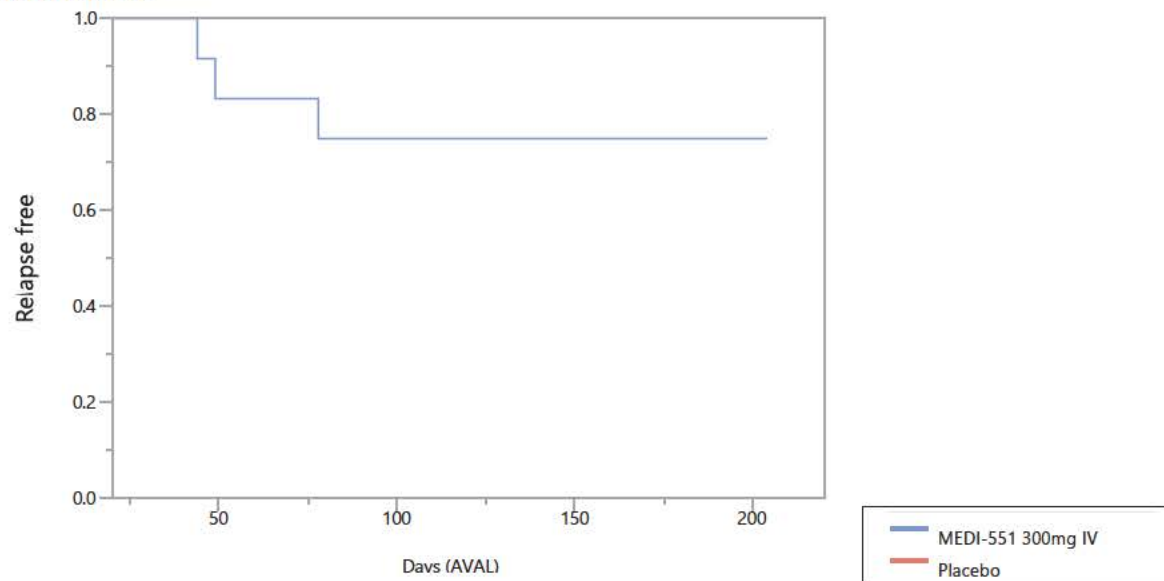
| Test     | ChiSquare | DF | Prob>ChiSq |
|----------|-----------|----|------------|
| Log-Rank | 26.0064   | 1  | <.0001*    |
| Wilcoxon | 23.1838   | 1  | <.0001*    |

**Source:** TTFE TTAA by AQP4IgG.jpg

**Figure 3: Time to first AC-confirmed relapse, AQP4-IgG negative subjects**

Product-Limit Survival Fit STRATA=AQP4-IgG seronegative

Survival Plot



### Summary

| Group             | Number failed | Number censored |
|-------------------|---------------|-----------------|
| MEDI-551 300mg IV | 3             | 10              |
| Placebo           | 0             | 4               |
| Combined          | 3             | 14              |

### Tests Between Groups

| Test     | ChiSquare | DF | Prob>ChiSq |
|----------|-----------|----|------------|
| Log-Rank | 1.0965    | 1  | 0.2950     |
| Wilcoxon | 1.0909    | 1  | 0.2963     |

Source: TTFE TTAA by AQP4IgG.jrp

*Reviewer Comment: Note that the p-value suggests a trend in favor of the placebo group. There is no indication that inebilizumab is effective in anti-AQP4 IgG seronegative patients.*

### Primary Endpoint by Additional Subgroups

Analysis of the primary endpoint for other key subgroups is shown in [Table 22](#). The unadjusted odds ratio favors inebilizumab for all subgroups except the anti-AQP4 IgG seronegative group.

**Table 22: Primary endpoint analysis by subgroups**

| Group                                           | n   | Inebilizumab | Placebo | Unadjusted OR | P value*       |
|-------------------------------------------------|-----|--------------|---------|---------------|----------------|
| All                                             | 230 | 0.121        | 0.393   | 0.212         | <0.0001        |
| Anti-AQP4 IgG                                   |     |              |         |               |                |
| Positive                                        | 213 | 0.112        | 0.423   | 0.172         | <0.0001        |
| Negative                                        | 17  | 0.231        | 0       |               | Favors Placebo |
| Sex                                             |     |              |         |               |                |
| F                                               | 209 | 0.079        | 0.400   | 0.191         | <0.0001        |
| M                                               | 21  | 0.200        | 0.333   | 0.800         | 0.4529         |
| Region                                          |     |              |         |               |                |
| Europe & Israel                                 | 94  | 0.093        | 0.316   | 0.223         | 0.014          |
| North America                                   | 43  | 0.097        | 0.250   | 0.322         | 0.1512         |
| Pan-Pacific & Asia                              | 51  | 0.191        | 0.556   | 0.188         | 0.0219         |
| ROW                                             | 42  | 0.115        | 0.500   | 0.130         | 0.0088         |
| Prior Prevent NMO Attack Med Category (NMOPCAT) |     |              |         |               |                |
| No                                              | 78  | 0.100        | 0.333   | 0.222         | 0.0134         |
| Yes                                             | 152 | 0.132        | 0.421   | 0.209         | 0.0002         |
| Race                                            |     |              |         |               |                |
| White                                           | 120 | 0.109        | 0.357   | 0.219         | 0.0022         |
| Asian                                           | 47  | 0.180        | 0.625   | 0.131         | 0.0058         |
| Age Group                                       |     |              |         |               |                |
| <40                                             | 138 | 0.122        | 0.323   | 0.290         | 0.008          |
| ≥40                                             | 92  | 0.119        | 0.480   | 0.147         | 0.0003         |

\*: nominal p-value from the Kaplan-Meier model, log-rank test

### Sensitivity Analyses

The increase in time to the first attack with inebilizumab treatment remains statistically significant if all subject-reported or all investigator-reported attacks are included in the analysis. The same is true if only AC-unanimous attacks are included. If subjects who discontinued prematurely are assumed to have had a relapse, the result also remains statistically significant. If subjects who had an attack within the first 15 days are censored in consideration of the use of corticosteroids for all subjects during that period of time, the delay to first AC-confirmed attack remains significant ([Table 23](#)).

**Table 23: Sensitivity analyses of the primary endpoint**

| Attack Analysis | Inebilizumab     | Placebo          | Unadjusted OR | P value* |
|-----------------|------------------|------------------|---------------|----------|
|                 | Attacks:censored | Attacks:censored |               |          |
| AC determined   | 21:153           | 22:34            | 0.212         | <0.0001  |
| AC unanimous    | 16:158           | 18:38            | 0.213         | <0.0001  |

| Attack Analysis                 | Inebilizumab     | Placebo          | Unadjusted | P value* |
|---------------------------------|------------------|------------------|------------|----------|
|                                 | Attacks:censored | Attacks:censored | OR         |          |
| Investigator determined         | 26:148           | 23:33            | 0.252      | <0.0001  |
| Subject reported                | 34:140           | 25:31            | 0.301      | 0.0002   |
| AC or premature d/c             | 26:148           | 22:34            | 0.272      | <0.0001  |
| Attacks at ≤ 15 day censored*** | 19:155           | 19:37            | 0.240      | <0.0001  |

Source: ADTTE by PARAM

\*\* : Time to AC-determined Attack or Premature Discontinuation from RCP (days)

\*\*\* : Time to AC-determined NMO Attacks: Subjects with AC-determined attacks before/on Day 15 are censored at the time of the attack (days)

## Data Quality and Integrity

There were no concerns for the quality or integrity of the data submitted.

## Efficacy Results – Secondary and other relevant endpoints

### Worsening from Baseline in EDSS Score

Worsening from baseline in EDSS score was defined as:

- (1) Worsening of 2 or more points in EDSS score for subjects with baseline score of 0
- (2) Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5
- (3) Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.

*Reviewer Comment: Note that the criteria require only a one-time increment in EDSS rather than confirmation of the criterion met after some interval such as after 3 or 6 months.*

*Reviewer Comment: The sponsor analyzed this endpoint using a logistic regression model and imputed worsening for those with a missing value. The following analyses are simple proportions and unadjusted odds ratios performed by this reviewer.*

The proportion of subjects who met one of the criteria for progression during the RCP by visit and treatment group is shown in [Table 24](#). An increment in disability is expected at the time of an attack. To assess the effect on disability not related to an acute attack, the analysis was limited to the non-attack routine visits, i.e. the visits at day 85 and day 197/early discontinuation visit.

**Table 24: Proportion of subjects meeting criteria for EDSS progression, by visit during the RCP**

| Visit Name          | MEDI-551 300mg IV | Placebo     |
|---------------------|-------------------|-------------|
| ATTACK              | 22 (12.6%)        | 17 (30.4%)  |
| DAY 85              | 16 (9.2%)         | 7 (12.5%)   |
| DAY 197/EDV         | 6 (3.4%)          | 2 (3.6%)    |
| ATTACK FOLLOW-UP    | 2 (1.1%)          | 4 (7.1%)    |
| SCREENING           | 1 (0.6%)          | 0 (0.0%)    |
| Subjects(filtered)  | 38 (21.8%)        | 25 (44.6%)  |
| 1stCollItemSubjects | 174 (100.0%)      | 56 (100.0%) |

Source: JRevSelADSLITFL\_Y VISITNAMEbyTRT01PfiltEPOCH\_RCP CRIT1FL\_Y

The last visit was either an attack visit or an attack follow-up visit in 41.1% of the placebo group but in only 13.7% of the inebilizumab group [Table 25](#).

**Table 25: Latest visit in the RCP by type of visit, mITT**

| VISIT            | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|------------------|-------|--------|-------------------|--------|---------|--------|
|                  | N     | %      | N                 | %      | N       | %      |
| ATTACK           | 31    | 13.5%  | 14                | 8.0%   | 17      | 30.4%  |
| ATTACK FOLLOW-UP | 16    | 7.0%   | 10                | 5.7%   | 6       | 10.7%  |
| DAY 1            | 15    | 6.5%   | 13                | 7.5%   | 2       | 3.6%   |
| DAY 197/EDV      | 118   | 51.3%  | 95                | 54.6%  | 23      | 41.1%  |
| DAY 85           | 45    | 19.6%  | 37                | 21.3%  | 8       | 14.3%  |
| SCREENING        | 2     | 0.9%   | 2                 | 1.1%   | 0       | 0.0%   |
| UNSCHEDULED      | 3     | 1.3%   | 3                 | 1.7%   | 0       | 0.0%   |
| Total            | 230   | 100.0% | 174               | 100.0% | 56      | 100.0% |

Source: Join EPOCH\_RCT c ADYmax TRT01P By (VISIT)

*Reviewer Comment: Inclusion of all visits in this endpoint results in a misleading result that implies that treatment with inebilizumab has an effect on disability independent of the reduction in relapses. Therefore, this reviewer analysis is limited to the non-attack visits.*

The proportion of subjects who met criteria for progression at the latest non-attack visit is shown in [Table 26](#). Relatively few subjects met the criteria in either treatment group. The proportion for those who were AQP4-IgG positive is shown in [Table 27](#).

**Table 26: Proportion of subjects who met criteria for EDSS progression at latest non-attack visit during the RCP, mITT**

| CRIT1FL | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|---------|-------|--------|-------------------|--------|---------|--------|
|         | N     | %      | N                 | %      | N       | %      |
| N       | 170   | 92.9%  | 134               | 93.7%  | 36      | 90.0%  |
| Y       | 13    | 7.1%   | 9                 | 6.3%   | 4       | 10.0%  |
| Total   | 183   | 100.0% | 143               | 100.0% | 40      | 100.0% |

Source: Join Day 85 and Day 197EDV subset of RCT with ADYmax TRT01P By (CRIT1FL)

**Table 27: Proportion of subjects who met criteria for EDSS progression at latest non-attack visit during the RCP, anti-AQP4-IgG seropositive group, mITT**

| CRIT1FL | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|---------|-------|--------|-------------------|--------|---------|--------|
|         | N     | %      | N                 | %      | N       | %      |
| N       | 158   | 93.5%  | 125               | 94.0%  | 33      | 91.7%  |
| Y       | 11    | 6.5%   | 8                 | 6.0%   | 3       | 8.3%   |
| Total   | 169   | 100.0% | 133               | 100.0% | 36      | 100.0% |

Source: AQP4pos Subset of Join Day 85 and Day 197EDV subset of RCT with ADYmax TRT01P By (CRIT1FL)

*Reviewer Comment: The number of subjects in the analyses limited to non-attack visits is less than the number of subjects in the full ITT because some subjects in the ITT did not have an EDSS assessment after Day 0, either because the latest assessment was at the time of an attack or because they were discontinued after Day 0 without another assessment in the RCP. Many of these subjects had their next EDSS assessment at the beginning of the OLP or SFP.*

*Reviewer Comment: The relatively low proportion of subjects meeting the criteria for progression of EDSS is not unexpected because of the relatively short period of observation and because patients with NMOSD typically do not show the gradual progression of disability independent of relapses as seen in patients with MS.*

The proportion of subjects in the mITT who met criteria for progression of EDSS for all visits is shown in [Table 28](#) and for the subgroup who were AQP4-IgG positive in [Table 29](#). The subjects with a missing value did not have an EDSS assessment after day 0 and within the RCP.

**Table 28: Proportion of subjects meeting criteria for EDSS progression, all visits, mITT**

| CRIT1FL | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|---------|-------|--------|-------------------|--------|---------|--------|
|         | N     | %      | N                 | %      | N       | %      |
| missing | 15    | 6.5%   | 13                | 7.5%   | 2       | 3.6%   |
| N       | 174   | 75.7%  | 138               | 79.3%  | 36      | 64.3%  |
| Y       | 41    | 17.8%  | 23                | 13.2%  | 18      | 32.1%  |
| Total   | 230   | 100.0% | 174               | 100.0% | 56      | 100.0% |

Source: Join EPOCH\_RCT c ADYmax TRT01P By (CRIT1FL)

**Table 29: Proportion of subjects meeting criteria for EDSS progression, all visits, AQP4-IgG positive, mITT**

| CRIT1FL | Total |        | MEDI-551 300mg IV |        | Placebo |        |
|---------|-------|--------|-------------------|--------|---------|--------|
|         | N     | %      | N                 | %      | N       | %      |
| missing | 14    | 6.6%   | 12                | 7.5%   | 2       | 3.8%   |
| N       | 161   | 75.6%  | 128               | 79.5%  | 33      | 63.5%  |
| Y       | 38    | 17.8%  | 21                | 13.0%  | 17      | 32.7%  |
| Total   | 213   | 100.0% | 161               | 100.0% | 52      | 100.0% |

Source: STRATA\_AQP4pos Subset of Join EPOCH\_RCT c ADYmax TRT01P By (CRIT1FL)

*Reviewer Comment: The overall proportion with EDSS progression is clearly driven by the expected increase in EDSS at the time of an attack.*

The absolute change in EDSS score at the last non-attack visit for the treatment groups is shown in [Table 30](#) and the percent change from baseline in [Table 31](#). The changes are relatively small and the differences between treatment groups is not statistically significant.

**Table 30: Absolute change in EDSS at latest non-attack visit, mITT**

| TRT01P            | Change from Baseline |        |         |      |     |        |           |
|-------------------|----------------------|--------|---------|------|-----|--------|-----------|
|                   | N Rows               | Mean   | Std Dev | Min  | Max | Median | N Missing |
| MEDI-551 300mg IV | 143                  | -0.14* | 0.63    | -2.5 | 3   | 0      | 0         |
| Placebo           | 40                   | -0.11  | 0.583   | -2.5 | 1   | 0      | 0         |

Source: Join Day 85 and Day 197EDV subset of RCT with ADYmax CHG By (TRT01P).jmp

\*: p = 0.7871, unpaired t-test

**Table 31: Percent change in EDSS at latest non-attack visit, mITT**

| TRT01P            | Percent change from baseline |       |         |       |     |        |
|-------------------|------------------------------|-------|---------|-------|-----|--------|
|                   | N Rows                       | Mean  | Std Dev | Min   | Max | Median |
| MEDI-551 300mg IV | 143                          | -4.1* | 20      | -100  | 75  | 0      |
| Placebo           | 40                           | 0.88  | 26.7    | -62.5 | 100 | 0      |

Source: Join Day 85 and Day 197EDV subset of RCT with ADYmax PCTCHG by (TRT01P).jmp

\*: p = 0.1995, unpaired t-test

*Reviewer Comment: The data do not support a change in disability at the latest point in the RCP due to treatment with inebilizumab.*

### Low Contrast Visual Acuity

The change from baseline to the last non-attack visit in low contrast visual acuity was not statistically significant. The median change was 0 for both treatment groups (Table 32). The result was similar for the anti-AQP4 IgG seropositive group.

**Table 32: Change from baseline to last non-attack visit in Low-Contrast Visual Acuity binocular score**

| TRT01P            | Change from baseline |      |         |     |     |        |
|-------------------|----------------------|------|---------|-----|-----|--------|
|                   | N Rows               | Mean | Std Dev | Min | Max | Median |
| MEDI-551 300mg IV | 174                  | 0.22 | 6.07    | -20 | 22  | 0      |
| Placebo           | 56                   | 1.81 | 9.02    | -18 | 35  | 0      |

Source: Join EPOCH\_RCPsubsetPARAM\_OEVALCUsubsetADOE with ADYmax CHG By (TRT01P).jmp

### Cumulative total active MRI lesions

The cumulative number of “active” MRI lesions was significantly reduced with inebilizumab treatment (Table 33) including for the anti-AQP4 seropositive population (Table 34).

**Table 33: Cumulative total active MRI lesions during the RCP**

| TRT01P            | N Rows | AVAL  |         |     |     |        |
|-------------------|--------|-------|---------|-----|-----|--------|
|                   |        | Mean  | Std Dev | Min | Max | Median |
| MEDI-551 300mg IV | 174    | 0.75* | 1.07    | 0   | 6   | 0      |
| Placebo           | 56     | 1.32  | 1.5     | 0   | 5   | 1      |

Source: PARAM\_CNCUACT1 Subset of ADMO AVAL By (TRT01P).jmp

\*: nominal p-value = 0.0020, unpaired t-test

**Table 34: Cumulative total active MRI lesions during the RCP, anti-AQP4 IgG seropositive subjects**

| TRT01P            | N Rows | AVAL  |         |     |     |        |
|-------------------|--------|-------|---------|-----|-----|--------|
|                   |        | Mean  | Std Dev | Min | Max | Median |
| MEDI-551 300mg IV | 161    | 0.76* | 1.09    | 0   | 6   | 0      |
| Placebo           | 52     | 1.35  | 1.48    | 0   | 5   | 1      |

Source: STRATA\_SEROPOS Subset of PARAM\_CNCUACT1 Subset of ADMO By (TRT01P).jmp

\*: nominal p = 0.0023

### SF-36

There was no significant difference in the percent change from baseline to week 28 on the Physical Component Score (PCS) of the SF-36 (Table 35).

**Table 35: Percent change from baseline to week 28 in the physical component score of the SF-36**

| AVISIT  | N Rows  |         | Percent Change (PCHG) |         |         |         |         |         |
|---------|---------|---------|-----------------------|---------|---------|---------|---------|---------|
|         |         |         | Mean                  |         | SD      |         | Median  |         |
|         | MEDI551 | Placebo | MEDI551               | Placebo | MEDI551 | Placebo | MEDI551 | Placebo |
| Week 12 | 137     | 38      | 1.68                  | 1.86    | 21.1    | 13.3    | 0       | 0.1     |
| Week 28 | 85      | 20      | 4.71                  | 0.83    | 21.5    | 19      | 2.76    | 0.61    |

Source: PARAM\_PCS Subset of EPOCH\_RCP Subset of ADQSSF PCHGbyTRT01P By (AVISIT).jmp

### Pain

Subject-rated pain (all areas) on the 100-point Numerical Rating Scale was numerically lower in the group treated with inebilizumab but the difference was not statistically significant (not adjusted for multiplicity) (Table 36).

**Table 36: Change in NRS from baseline to last visit in RCT**

| TRT01P            | Percent Change |      |         |        |
|-------------------|----------------|------|---------|--------|
|                   | N              | MEAN | STD DEV | MEDIAN |
| MEDI-551 300MG IV | 123            | 38.8 | 165     | 0      |
| PLACEBO           | 44             | 96.4 | 271     | 0      |

Source: AVRGPAIN Last RCP Visit Subset Of ADQSPN PCHG By (TRT01P).Jmp

### Modified Rankin Score (mRS)

There was little change in the mRS from baseline to the last (non-attack) visit during the RCP (Table 37).

**Table 37: Change from baseline to last non-attack visit in the modified Rankin Scale score**

| VISIT       | AVAL minus baseline |         |         |         |         |         |         |
|-------------|---------------------|---------|---------|---------|---------|---------|---------|
|             | N                   | N       |         | Mean    |         | Median  |         |
|             | total               | MEDI551 | Placebo | MEDI551 | Placebo | MEDI551 | Placebo |
| DAY 197/EDV | 118                 | 94      | 24      | -0.1    | -0      | 0       | 0       |

EPOCH\_RCP Subset of ADQSRS AVALminusBASE By (VISIT) 2.jmp

### Annualized Relapse Rate

Because subjects who had an attack were discontinued from blinded treatment assignment, a valid estimate of the Annualized Relapse Rate (ARR) is not possible. Furthermore, the duration of observation is too short to estimate the ARR accurately. Nevertheless, the ARR was included as a secondary endpoint by the sponsor and is therefore calculated using the time on investigational treatment and the number of relapses that occurred up to the time of an attack or to the end of the RCP. The ARR is reduced with inebilizumab treatment for the overall mITT ([Table 38](#)) and for the anti-AQP4 seropositive population ([Table 39](#)).

**Table 38: Annualized Relapse Rate, mITT**

| Attack Analysis                 | Inebilizumab |       | Placebo |       |
|---------------------------------|--------------|-------|---------|-------|
|                                 | n            | ARR   | n       | ARR   |
| AC determined                   | 21           | 0.255 | 22      | 0.907 |
| AC unanimous                    | 16           | 0.194 | 18      | 0.742 |
| Investigator determined         | 26           | 0.303 | 23      | 0.949 |
| Subject reported                | 34           | 0.412 | 25      | 1.03  |
| AC or premature d/c             | 26           | 0.315 | 22      | 0.907 |
| Attacks at ≤ 15 day censored*** | 19           | 0.230 | 19      | 0.784 |

Source: ADTTE CSR by TRT01P By (PARAM).jmp

**Table 39: Annualized Relapse Rate, anti-AQP4 seropositive subjects**

| Attack Analysis                 | Inebilizumab |       | Placebo |       |
|---------------------------------|--------------|-------|---------|-------|
|                                 | n            | ARR   | n       | ARR   |
| AC determined                   | 18           | 0.234 | 22      | 1.00  |
| AC unanimous                    | 16           | 0.208 | 18      | 0.818 |
| Investigator determined         | 22           | 0.286 | 23      | 1.05  |
| Subject reported                | 30           | 0.390 | 24      | 1.09  |
| AC or premature d/c             | 22           | 0.286 | 22      | 1.00  |
| Attacks at ≤ 15 day censored*** | 16           | 0.208 | 19      | 0.864 |

Source: STRATA\_SEROPOS Subset of ADTTE CSR by TRT01P By (PARAM).jmp

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

### **Dose/Dose Response**

Only one dose was studied.

### **Durability of Response**

The durability of the response was not studied

### **Persistence of Effect**

The persistence of the treatment effect was not studied

### **Additional Analyses Conducted on the Individual Trial**

No additional efficacy analyses were conducted

## **7. Integrated Review of Effectiveness**

---

### **7.1. Assessment of Efficacy Across Trials**

A single trial was conducted.

#### **7.1.1. Primary Endpoints**

#### **7.1.2. Secondary and Other Endpoints**

#### **7.1.3. Subpopulations**

#### **7.1.4. Dose and Dose-Response**

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

Benefit in the postmarket setting has not been studied

#### **7.2.2. Other Relevant Benefits**

No additional benefits were demonstrated

### **7.3. Integrated Assessment of Effectiveness**

Not applicable

## 8. Review of Safety

### 8.1. Safety Review Approach

The primary analysis of safety includes subjects who participated in the randomized, placebo-controlled phase of the single trial in NMOSD. Additional exposure for NMOSD is available from those subjects treated with placebo during the randomized-controlled phase who entered the open label phase of the trial along with those treated with inebilizumab who also continued treatment in the OLE. Because there is no clear evidence that inebilizumab is effective for patients with NMOSD who are not seropositive for the anti-AQP4 IgG antibody, analyses limited to the seropositive population are also shown.

Two small phase 1 studies, one in patients with scleroderma and one in MS patients, were not pooled with the NMOSD study and are reviewed individually.

### 8.2. Review of the Safety Database

#### 8.2.1. Overall Exposure

One of 175 subjects randomized to inebilizumab was not treated. The number of subjects exposed to at least one dose of inebilizumab is shown in [Table 40](#).

**Table 40: Number of subjects exposed to inebilizumab**

| Population                              | Inebilizumab    | placebo |
|-----------------------------------------|-----------------|---------|
| Healthy volunteers                      | 0               | 0       |
| Controlled trials for NMOSD             | 174             | 56      |
| AQP4 IgG seropositive                   | 161             | 52      |
| Any exposure for NMOSD                  | 225             | -       |
| AQP4 IgG seropositive                   | 208             |         |
| Controlled trials for other indications |                 |         |
| Systemic Sclerosis                      | 28 <sup>1</sup> | 4       |
| Multiple Sclerosis                      | 21 <sup>2</sup> | 7       |

<sup>1</sup>: 0.1 mg/kg [n = 1], 0.3 mg/kg [n = 4], 1.0 mg/kg [n = 6], 3.0 mg/kg [n = 6], and 10.0 mg/kg [n = 7]

<sup>2</sup>: 30 mg IV [n = 6], 60 mg SC [n = 3], 100 mg IV [n = 3], 100 mg SC [n = 3], and 600 mg IV [n = 6]

### Exposure in the RCP

In the Randomized Controlled Phase (RCP), all subjects received the full first dose of assigned treatment. A full second dose was received by 169 of the 170 subjects continuing in the trial and randomized to inebilizumab. One inebilizumab subject did not receive the full second dose because of an abnormally high temperature but did go on to treatment with additional doses without incident. All 53 remaining subjects assigned to placebo received the full second dose.

The mean duration of exposure during the RCP was 0.47 years for the subjects randomized to inebilizumab and 0.43 years for those randomized to placebo ([Table 41](#)).

**Table 41: Duration of Treatment during the RCP, years, safety population**

| TRT01A                         | Treatment Duration in years in Period 1 (RCP) (TR01DURY) |      |         |      |      |        |      |
|--------------------------------|----------------------------------------------------------|------|---------|------|------|--------|------|
|                                | N                                                        | Mean | Std Dev | Min  | Max  | Median | Sum  |
| Full Safety population         |                                                          |      |         |      |      |        |      |
| INEBILIZUMAB 300mg IV          | 174                                                      | 0.47 | 0.15    | 0.04 | 0.67 | 0.54   | 82.5 |
| Placebo                        | 56                                                       | 0.43 | 0.17    | 0.07 | 0.64 | 0.53   | 24.3 |
| AQP4 IgG seropositive subjects |                                                          |      |         |      |      |        |      |
| MEDI-551 300mg IV              | 161                                                      | 0.48 | 0.15    | 0.04 | 0.67 | 0.54   | 76.9 |
| Placebo                        | 52                                                       | 0.42 | 0.17    | 0.07 | 0.64 | 0.53   | 22.0 |

Source: ASTRFL\_Y Subset of ADSL TR01DURY By (TRT01A).jmp

*Reviewer Comment: The duration of exposure using TR01DURY from the ADSL dataset assumes exposure to the drug from the date of first dose until the last day before the subject entered the OLP, SFP, EOS or as of the data cut-off date. The "extent of exposure" in the EX database assumes exposure from the date of the first dose to the date of the last dose plus 60 days, the latter representing 5 PK half-lives of inebilizumab. Since the PD duration is approximately 26 weeks or more, the calculation of treatment duration using the above variable is more representative than that in the EX database.*

### Any inebilizumab exposure

The population exposed to any dose of inebilizumab either in the RCP or in the Open Label Phase (OLP) at the time of submission consisted of 225 subjects with a mean duration of treatment of 1.59 years and 213 subjects seropositive for anti-AQP4 IgG antibody with a mean duration of exposure of 1.56 years ([Table 42](#)). The distribution of exposures for the full safety population is shown in [Figure 4](#) and for the anti-AQP4 IgG seropositive population in [Figure 5](#). At the time of the 120-day safety update the mean exposure was 2.12±1.08 years.

**Table 42: Duration of treatment, all inebilizumab population, safety population**

| Any inebilizumab treatment (TR03DURY) |      |         |      |      |        |     |
|---------------------------------------|------|---------|------|------|--------|-----|
| N                                     | Mean | Std Dev | Min  | Max  | Median | Sum |
| Safety Population                     |      |         |      |      |        |     |
| 225                                   | 1.59 | 1.01    | 0.02 | 3.71 | 1.54   | 358 |
| Anti-AQP4 IgG seropositive subjects   |      |         |      |      |        |     |
| 213                                   | 1.56 | 1       | 0.02 | 3.61 | 1.49   | 324 |

Source: Summary of TR03DURY ANYMDFL\_Y Subset of ADSL.jmp

**Figure 4: Duration of treatment, years, any inebilizumab population, safety population**

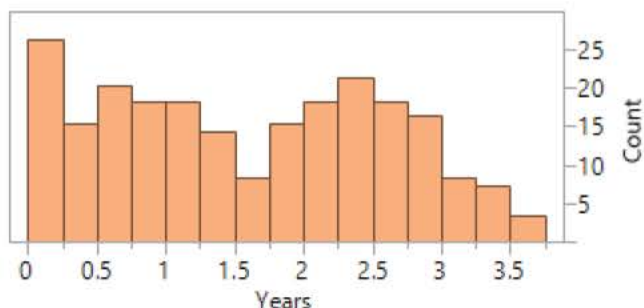
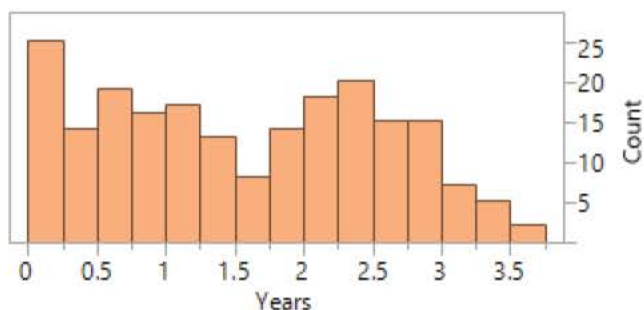


**Figure 5: Duration of treatment, years, any inebilizumab, anti-AQP4 IgG seropositive subjects**



At the time of submission, 184 subjects (169 seropositive) had been treated with inebilizumab for 6 months or more; 146 (134 seropositive) had been treated for one year or more. At the time of the 4-month safety update, 217 subjects (202 seropositive) had been treated for 6 months or more; 182 (167 seropositive) had been treated for one year or more ([Table 43](#)).

**Table 43: Duration of treatment, all inebilizumab population**

| Exposure Duration, years | Safety Population |                  | Anti-AQP4 IgG seropositive |                  |
|--------------------------|-------------------|------------------|----------------------------|------------------|
|                          | At submission     | At safety update | At submission              | At safety update |
| ≤ 0.5                    | 41                | 8                | 39                         | 6                |
| ≥ 0.5                    | 184               | 217              | 169                        | 202              |
| ≥ 1                      | 146               | 182              | 134                        | 167              |

| Exposure<br>Duration, years | Safety Population |                  | Anti-AQP4 IgG seropositive |                  |
|-----------------------------|-------------------|------------------|----------------------------|------------------|
|                             | At submission     | At safety update | At submission              | At safety update |
| ≥ 1.5                       | 114               | 146              | 104                        | 133              |
| ≥ 2.0                       | 91                | 118              | 82                         | 107              |
| ≥ 2.5                       | 52                | 94               | 44                         | 85               |
| ≥ 3.0                       | 18                | 57               | 14                         | 49               |
| ≥ 3.5                       | 3                 | 23               | 2                          | 18               |
| ≥ 4.0                       | 0                 | 7                | 0                          | 5                |

Source: ASTRFL\_Y subset ADSL, TR03DURY

*Reviewer Comment: When limited to the AQP4 IgG seropositive population, there remain over 100 subjects exposed for 1 year or more.*

### 8.2.2. Relevant characteristics of the safety population:

The demographics for the safety population, which does not include one subject from the full ITT, is shown in [Table 44](#) and for the population seropositive for anti-AQP4 IgG in [Table 45](#).

**Table 44: Demographics, full safety population**

| Subgroup                          | MEDI-551 300mg IV<br>(N = 174)<br>n (%) | Placebo<br>(N = 56)<br>n (%) | Total<br>(N = 230)<br>n (%) |
|-----------------------------------|-----------------------------------------|------------------------------|-----------------------------|
| Sex                               |                                         |                              |                             |
| Female                            | 159 (91.4)                              | 50 (89.3)                    | 209 (90.9)                  |
| Male                              | 15 (8.6)                                | 6 (10.7)                     | 21 (9.1)                    |
| Age                               |                                         |                              |                             |
| Mean                              | 42.99                                   | 42.59                        | 42.9                        |
| Standard Deviation                | 11.56                                   | 13.93                        | 12.15                       |
| Minimum                           | 18                                      | 18                           | 18                          |
| Median                            | 43                                      | 42.5                         | 43                          |
| Maximum                           | 73                                      | 74                           | 74                          |
| Age Group                         |                                         |                              |                             |
| Age Group 1 (AGE < 40)            | 67 (38.5)                               | 25 (44.6)                    | 92 (40.0)                   |
| Age Group 2 (40 <= AGE)           | 107 (61.5)                              | 31 (55.4)                    | 138 (60.0)                  |
| Race                              |                                         |                              |                             |
| American Indian or Alaskan Native | 14 (8.0)                                | 5 (8.9)                      | 19 (8.3)                    |
| Asian                             | 39 (22.4)                               | 8 (14.3)                     | 47 (20.4)                   |
| Black or African American         | 15 (8.6)                                | 5 (8.9)                      | 20 (8.7)                    |
| Multiple Categories Checked       | 1 (0.6)                                 | 0 (0.0)                      | 1 (0.4)                     |

| Subgroup               | MEDI-551 300mg IV<br>(N = 174)<br>n (%) | Placebo<br>(N = 56)<br>n (%) | Total<br>(N = 230)<br>n (%) |
|------------------------|-----------------------------------------|------------------------------|-----------------------------|
| Other                  | 13 (7.5)                                | 10 (17.9)                    | 23 (10.0)                   |
| White                  | 92 (52.9)                               | 28 (50.0)                    | 120 (52.2)                  |
| Ethnicity              |                                         |                              |                             |
| Hispanic or Latino     | 28 (16.1)                               | 15 (26.8)                    | 43 (18.7)                   |
| Not Hispanic or Latino | 146 (83.9)                              | 41 (73.2)                    | 187 (81.3)                  |
| Region                 |                                         |                              |                             |
| Africa                 | 1 (0.6)                                 | 3 (5.4)                      | 4 (1.7)                     |
| Asia                   | 46 (26.4)                               | 7 (12.5)                     | 53 (23.0)                   |
| Canada                 | 2 (1.1)                                 | 0 (0.0)                      | 2 (0.9)                     |
| Europe                 | 71 (40.8)                               | 19 (33.9)                    | 90 (39.1)                   |
| Other                  | 0 (0.0)                                 | 2 (3.6)                      | 2 (0.9)                     |
| South America          | 25 (14.4)                               | 13 (23.2)                    | 38 (16.5)                   |
| United States          | 29 (16.7)                               | 12 (21.4)                    | 41 (17.8)                   |

Source: LDR2020-01-28\_DEMTOOL ASTRTFL\_Y

**Table 45: Demographics, safety population seropositive for anti-AQP4 IgG**

| Subgroup                          | MEDI-551 300mg IV<br>(N = 161)<br>n (%) | Placebo<br>(N = 52)<br>n (%) | Total<br>(N = 213)<br>n (%) |
|-----------------------------------|-----------------------------------------|------------------------------|-----------------------------|
| Sex                               |                                         |                              |                             |
| Female                            | 151 (93.8)                              | 49 (94.2)                    | 200 (93.9)                  |
| Male                              | 10 (6.2)                                | 3 (5.8)                      | 13 (6.1)                    |
| Age                               |                                         |                              |                             |
| Mean                              | 43.17                                   | 42.42                        | 42.99                       |
| Standard Deviation                | 11.59                                   | 14.33                        | 12.29                       |
| Minimum                           | 18                                      | 18                           | 18                          |
| Median                            | 43                                      | 43                           | 43                          |
| Maximum                           | 73                                      | 74                           | 74                          |
| Age Group                         |                                         |                              |                             |
| Age Group 1 (AGE < 40)            | 61 (37.9)                               | 24 (46.2)                    | 85 (39.9)                   |
| Age Group 2 (40 <= AGE)           | 100 (62.1)                              | 28 (53.8)                    | 128 (60.1)                  |
| Race                              |                                         |                              |                             |
| American Indian or Alaskan Native | 11 (6.8)                                | 5 (9.6)                      | 16 (7.5)                    |

| Subgroup                    | MEDI-551 300mg IV<br>(N = 161)<br>n (%) | Placebo<br>(N = 52)<br>n (%) | Total<br>(N = 213)<br>n (%) |
|-----------------------------|-----------------------------------------|------------------------------|-----------------------------|
| Asian                       | 37 (23.0)                               | 8 (15.4)                     | 45 (21.1)                   |
| Black or African American   | 14 (8.7)                                | 5 (9.6)                      | 19 (8.9)                    |
| Multiple Categories Checked | 1 (0.6)                                 | 0 (0.0)                      | 1 (0.5)                     |
| Other                       | 12 (7.5)                                | 10 (19.2)                    | 22 (10.3)                   |
| White                       | 86 (53.4)                               | 24 (46.2)                    | 110 (51.6)                  |
| Ethnicity                   |                                         |                              |                             |
| Hispanic or Latino          | 25 (15.5)                               | 15 (28.8)                    | 40 (18.8)                   |
| Not Hispanic or Latino      | 136 (84.5)                              | 37 (71.2)                    | 173 (81.2)                  |
| Region                      |                                         |                              |                             |
| Africa                      | 1 (0.6)                                 | 3 (5.8)                      | 4 (1.9)                     |
| Asia                        | 43 (26.7)                               | 7 (13.5)                     | 50 (23.5)                   |
| Canada                      | 2 (1.2)                                 | 0 (0.0)                      | 2 (0.9)                     |
| Europe                      | 66 (41.0)                               | 16 (30.8)                    | 82 (38.5)                   |
| Other                       | 0 (0.0)                                 | 2 (3.8)                      | 2 (0.9)                     |
| South America               | 22 (13.7)                               | 13 (25.0)                    | 35 (16.4)                   |
| United States               | 27 (16.8)                               | 11 (21.2)                    | 38 (17.8)                   |

Source: LDR2020-01-28\_DEMTOOL ASTRTFL\_Y AQP4pos

*Reviewer Comment: The demographic characteristics of the anti-AQP4 IgG seropositive population are generally similar to those in the study of Soliris for the treatment of NMOSD. There are slightly more subjects of the white race and slightly fewer Asian subjects in this study. There is a lower proportion of subjects from the US and Asia with a higher proportion from Europe.*

### 8.2.3. Adequacy of the safety database:

The number of subjects exposed to any inebilizumab is relatively small at 225. There are 217 subjects exposed for at least 6 months, fewer than the 300 to 600 recommended in ICH E1<sup>1</sup>. The mean and median exposure when there was a placebo comparator was only approximately 6 months. However, there are more than 100 subjects exposed to inebilizumab for at least one year, the recommended minimum.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

<sup>1</sup> [https://database.ich.org/sites/default/files/E1\\_Guideline.pdf](https://database.ich.org/sites/default/files/E1_Guideline.pdf)

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no significant issues of data integrity or quality.

### 8.3.2. Categorization of Adverse Events

Adverse events were categorized using standard MedDRA terms and groupings.

### 8.3.3. Routine Clinical Tests

Routine safety laboratory studies including chemistries, hematology studies and ECG collection were adequate. Special laboratory studies related to the target of the investigational drug were adequate.

## 8.4. Safety Results

### 8.4.1. Deaths

There were 2 deaths during the trial, neither during the RCP. Both occurred during treatment with inebilizumab, one during the OLP and one during the Safety Follow-up period.

Subject (b) (6)

This 31-year old male was randomized into the RCP and started treatment with placebo on (b) (6). He had been treated with corticosteroids for an NMO relapse in 1996, 2000, 2007, 2008, 2010, and in April of 2015. He had also been treated continuously with corticosteroids from 1989 to 1991. Baseline laboratory studies were normal, with the exception of slightly elevated leukocyte and neutrophil counts, both of which were further elevated on study day 1. An SAE of pneumonia started on study day 4 after the first infusion of placebo followed by complete recovery after inpatient treatment with antibiotics. A protocol-defined relapse occurred on (b) (6) (study day 29), manifested primarily by increased leg weakness and loss of bladder control. EDSS had increased to 8.0. Intravenous methylprednisolone was administered for 5 days and the subject chose to enter the open label phase of the study. The first dose of inebilizumab was administered on (b) (6). CBC and chemistries were reported to be normal on that day. On (b) (6) it was reported that the subject was weak and had a poor appetite. On (b) (6) the subject's mother found him unresponsive and not breathing. He was pronounced dead at home on that day. There were no recent laboratory studies. No autopsy was performed.

*Reviewer Comment: There is no indication that this sudden death was related to treatment with inebilizumab. The proximity in time to the most recent infusion raises a concern for a reaction to the drug but there are no other*

*features to suggest an infusion reaction. The nature of the new neurologic symptoms suggests a new lesion in the cervical spinal cord and/or brainstem.*

Subject (b) (6)

This 68-year old female was randomized and started treatment with inebilizumab on (b) (6). Screening laboratory studies were unremarkable. No attacks occurred during the RCP and the subject entered the OLP on (b) (6). Past medical history included chronic bronchitis, osteoarthritis, and trigeminal neuralgia. An attack of myelitis had occurred in 2013, 2 attacks in 2014, and one in 2015. She had been treated with azathioprine, 50 mg per day until March, 2016. Concomitant medications at the time of a series of SAEs were carbamazepine, gabapentin, amitriptyline, ketoprofen, nitrofurantoin, omeprazole, tramadol, acetaminophen, and acetylsalicylic acid. On (b) (6) this subject experienced blurred vision with decreased visual acuity in the left eye. An Optic Neuritis attack was confirmed that was treated with IV methylprednisolone, 1 gram daily for 4 days, with limited recovery of visual function. The EDSS score on attack assessment was 7. An attack follow-up visit was done on (b) (6). The investigator stated that no new significant neurological findings were noted during this visit with no change in the EDSS score (remained at 7). (The (b) (4) clinical team reviewed the brain and optic nerve MRI images from the attack visit on (b) (6) (pre-contrast, post contrast and FLAIR sequences) and determined that there was no evidence of white matter lesions suggesting underlying brain pathology at the time of the attack assessment). On (b) (6) the subject entered the OLP and received 1 dose of inebilizumab. The neurological and physical examination and EDSS remained the same as the previous attack follow-up visit. Laboratory findings including chemistry, electrolytes and hematology performed during the attack visit, follow-up visit, and OLP visit were within normal limits. No additional inebilizumab doses had been administered. On (b) (6) study day 222 and 3 days after the most recent infusion of inebilizumab, she was hospitalized for an NMO attack that was considered life-threatening. At the time of the attack CD19+ B-cells were 0.762 cells/ $\mu$ L (219 cells/ $\mu$ L at baseline). Over the next 2 to 3 days she became less interactive and somnolent. On (b) (6) the family noted that she was not speaking and had weakness of her right side. A CT scan in the hospital emergency room showed a hypodense lesion in the left fronto-parietal region. The neurologic deficits remained unchanged until two generalized motor seizures occurred on (b) (6). Decorticate posturing was noted at that time. Respiratory compromise required intubation, which was followed by a cardio-respiratory arrest. A CT scan at that time revealed new hypodense lesions in the right parietal region and bilaterally in white matter. PML was suspected. A lumbar puncture revealed no abnormal findings, with the exception of a few bacteria on gram stain which were considered contaminants. One laboratory reported that JC virus was not detected in the CSF but another reported detectable JC virus. The sample was subsequently tested at the National Institutes of Health - no JC virus was detected. A brain MRI on (b) (6) revealed "pre- and post-gadolinium multiple T2/FLAIR hyperintense lesions in the

left inferior frontal region extending to the left lentiform nucleus and head of the caudate nucleus, in the white matter of the left frontal and parietal lobe, in the genu and posterior limb of the left internal capsule, in the right parietal white matter and left parietal white matter". Sparing of the U-fibers and cortical grey matter was reported. No edema or significant contrast enhancement were reported. Increased respiratory difficulty occurred on (b) (6) and the subject died on that day. The family declined to permit an autopsy.

***Reviewer Comment: Updated clinical information and any additional laboratory or imaging data were requested. The response, in sequence 0017, indicated that there was no additional clinical information.***

The eligibility scan showed no changes that would be consistent with MS. This scan was re-reviewed and was reported to show "Multiple hyperintense small lesions involving the subcortical white matter in the frontal and parietal regions and in the periventricular white matter. No pathological enhancement. No other abnormality noted.

There were no changes on a scan performed on (b) (6). This scan was also re-reviewed and was reported to show "In comparison with the previous study one lesion in the left frontal subcortical white matter has progressed in size. Two new lesions, hyperintense in FLAIR are seen: one in the right thalamus, the other in the left frontal subcortical white matter". None of the lesions noted is enhancing.

An MRI scan performed on (b) (6) reported "Large lesions with increased signal intensity in T2 and Flair involving the right parietal white matter, the left frontal and left parietal white matter extending to the corpus callosum. The lesions described are suggestive of ADEM (acute disseminated encephalomyelitis)". This scan was also re-reviewed and reported to show:

Evidence of multiple lesions hyperintense on FLAIR in the following locations:  
-left inferior frontal region extending to the left lentiform nucleus and head of the caudate nucleus;  
-in the white matter of the left frontal and parietal lobe;  
-in the genu and posterior limb of the left internal capsule;  
-in the right parietal white matter;  
-in the splenium of the corpus callosum on the left side.

Following injection of gadolinium, the sequence is limited due to movement of the subject, however three enhancing areas of a few millimeters (2-3mm) are noted in the right parietal white matter and one focal enhancement (5mm) is seen in the left frontal white matter.

Conclusion:

Multiple confluent hyper-intense lesions affecting the white matter and also the deep grey matter, have developed since the MRI of (b) (6). In view of the clinical information received, PML has to be considered. However, a number of features argue against this diagnosis; the lesions are extremely large and confluent, the basal ganglia are involved, the U-fibres and cortical gray matter tend to be spared, and there are a few areas of contrast enhancement. The MRI appearance alone is more consistent with an acute demyelinating syndrome such as ADEM, although this may be less likely in the clinical context. Finally, the possibility of IRIS is unlikely due to the lack of oedema, mass effect and typical enhancement.

The second review was performed by D. Tampieri MD, FRCPC

*Reviewer Comment: See the discussion of possible PML in Section 8.5.1*

#### 8.4.2. Serious Adverse Events

For the complete safety population, an SAE occurred during the RCP in 8 subjects (4.6%) treated with inebilizumab and in 5 subjects (8.9%) treated with placebo (Table 46). Treatment-emergent SAEs for the anti-AQP4 IgG seropositive population are listed in Table 47.

*Reviewer Comment: None of the SAEs in the inebilizumab group raise a serious safety concern. However, the number of patients treated was relatively small and the duration of treatment was relatively short. Continued surveillance for the same adverse events known to occur with other drugs that target B cells will be appropriate.*

**Table 46: Serious Adverse Events during the RCP, by SOC and Preferred Term, safety population**

| Body System or Organ Class                           | Dictionary Derived Term   | INEBILIZUMAB<br>300mg IV | Placebo  |
|------------------------------------------------------|---------------------------|--------------------------|----------|
| Eye disorders                                        | Vision blurred            | 1 (0.6%)                 | 0 (0.0%) |
|                                                      | Visual acuity reduced     | 0 (0.0%)                 | 1 (1.8%) |
| Gastrointestinal disorders                           | Diarrhoea                 | 1 (0.6%)                 | 0 (0.0%) |
| General disorders and administration site conditions | Chest pain                | 0 (0.0%)                 | 1 (1.8%) |
| Hepatobiliary disorders                              | Cholangitis acute         | 1 (0.6%)                 | 0 (0.0%) |
|                                                      | Cholecystitis acute       | 1 (0.6%)                 | 0 (0.0%) |
|                                                      | Hepatic function abnormal | 1 (0.6%)                 | 0 (0.0%) |
| Infections and infestations                          | Atypical pneumonia        | 1 (0.6%)                 | 0 (0.0%) |
|                                                      | Meningitis viral          | 0 (0.0%)                 | 1 (1.8%) |
|                                                      | Myelitis                  | 1 (0.6%)                 | 0 (0.0%) |
|                                                      | Pneumonia                 | 0 (0.0%)                 | 1 (1.8%) |

| Body System or Organ Class                      | Dictionary Derived Term | INEBILIZUMAB<br>300mg IV | Placebo     |
|-------------------------------------------------|-------------------------|--------------------------|-------------|
|                                                 | Septic shock            | 0 (0.0%)                 | 1 (1.8%)    |
|                                                 | Urinary tract infection | 1 (0.6%)                 | 0 (0.0%)    |
| Injury, poisoning and procedural complications  | Burns third degree      | 1 (0.6%)                 | 0 (0.0%)    |
| Metabolism and nutrition disorders              | Hypoglycaemia           | 0 (0.0%)                 | 1 (1.8%)    |
| Musculoskeletal and connective tissue disorders | Arthralgia              | 1 (0.6%)                 | 0 (0.0%)    |
| Nervous system disorders                        | Migraine                | 0 (0.0%)                 | 1 (1.8%)    |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea                | 0 (0.0%)                 | 1 (1.8%)    |
| Total subjects with an SAE                      | Subjects(filtered)      | 8 (4.6%)                 | 5 (8.9%)    |
| Total subjects                                  | 1stCollItemSubjects     | 174 (100.0%)             | 56 (100.0%) |

Source: JRevSelADSLASTRFL\_Y AEDECODbySOCbyTRT01AfiltTRTEMFL\_Y EPOCH\_RCT AESER\_Y

**Table 47: Serious Adverse Events during the RCP, by SOC and Preferred Term, safety population, anti-AQP4 IgG seropositive subjects**

| Body System or Organ Class                           | Dictionary Derived Term                | MEDI-551<br>300mg IV | Placebo     |
|------------------------------------------------------|----------------------------------------|----------------------|-------------|
| Eye disorders                                        | Visual acuity reduced                  | 0 (0.0%)             | 1 (1.9%)    |
| Gastrointestinal disorders                           | Diarrhoea                              | 1 (0.6%)             | 0 (0.0%)    |
| General disorders and administration site conditions | Chest pain                             | 0 (0.0%)             | 1 (1.9%)    |
| Hepatobiliary disorders                              | Cholangitis acute                      | 1 (0.6%)             | 0 (0.0%)    |
|                                                      | Cholecystitis acute                    | 1 (0.6%)             | 0 (0.0%)    |
|                                                      | Hepatic function abnormal              | 1 (0.6%)             | 0 (0.0%)    |
| Infections and infestations                          | Atypical pneumonia                     | 1 (0.6%)             | 0 (0.0%)    |
|                                                      | Meningitis viral                       | 0 (0.0%)             | 1 (1.9%)    |
|                                                      | Pneumonia                              | 0 (0.0%)             | 1 (1.9%)    |
|                                                      | Septic shock                           | 0 (0.0%)             | 1 (1.9%)    |
| Injury, poisoning and procedural complications       | Burns third degree                     | 1 (0.6%)             | 0 (0.0%)    |
| Metabolism and nutrition disorders                   | Hypoglycaemia                          | 0 (0.0%)             | 1 (1.9%)    |
| Musculoskeletal and connective tissue disorders      | Arthralgia                             | 1 (0.6%)             | 0 (0.0%)    |
| Nervous system disorders                             | Migraine                               | 0 (0.0%)             | 1 (1.9%)    |
|                                                      | Myelitis transverse                    | 1 (0.6%)             | 0 (0.0%)    |
|                                                      | Neuromyelitis optica spectrum disorder | 1 (0.6%)             | 0 (0.0%)    |
| Respiratory, thoracic and mediastinal disorders      | Dyspnoea                               | 0 (0.0%)             | 1 (1.9%)    |
| Total subjects with an SAE                           | Subjects(filtered)                     | 7 (4.3%)             | 5 (9.6%)    |
| Total subjects                                       | 1stCollItemSubjects                    | 161 (100.0%)         | 52 (100.0%) |

Source: JRevSel ADL ASTRTFL\_Y STRATA\_SEROPOS SOCbyAEDECODbyADSLTRT01AfiltAESER\_Y TRTEMFL\_Y EPOCH\_RCP

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

An adverse event that led to discontinuation of study drug during the RCP occurred in two inebilizumab subjects and in no placebo subjects ([Table 48](#)).

**Table 48: Adverse events that led to discontinuation of study drug, As Treated population**

| Dictionary Derived Term | INEBILIZUMAB 300mg IV |
|-------------------------|-----------------------|
| Atypical pneumonia      | 1 (0.6%)              |
| Myasthenia gravis       | 1 (0.6%)              |
| Subjects(filtered)      | 2 (1.1%)              |
| 1stCollItemSubjects     | 174 (100.0%)          |

Source: JRevSelADSL ASTRFTL\_Y AEDECODbyADSL TRT01AfilTANL01FL\_Y ACTION\_DC

#### 8.4.4. Significant Adverse Events

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

##### Adverse Events During the RCP

The most common treatment emergent adverse events during the RCP are shown in [Table 49](#). Shaded rows represent those that occurred in 2% or more of the inebilizumab population and also more frequently than in the placebo. Any adverse event occurred in 125 subjects treated with inebilizumab (71.8%) and in 41 subjects treated with placebo (73.2%). The overall rate of adverse events per subject year of exposure was 1.52 for those treated with inebilizumab and 1.69 for those treated with placebo. The comparable table limited to the anti-AQP4 IgG seropositive population is [Table 50](#).

*Reviewer Comment: The changes in the incidence of AEs when limited to the AQP4 IgG seropositive population do not appear to be significant.*

The most common adverse events by SOC were infections and infestations ([Table 51](#); [Table 52](#) for the AQP4 IgG seropositive population). No opportunistic infections occurred in either group. No single type of infection was notably more prominent in the inebilizumab group.

*Reviewer Comment: Arthralgia and other types of musculoskeletal pain are more common in the inebilizumab group. The same is true for the FDA/ODE1 AE grouping of arthralgia, arthritis and arthrosis ([Table 54](#)).*

**Table 49: Treatment Emergent Adverse Events during RCP, Preferred Term, >2% of inebilizumab population, (greater than placebo shaded), safety population**

| Dictionary Derived Term   | INEBILIZUMAB 300mg IV | Placebo   |
|---------------------------|-----------------------|-----------|
| Urinary tract infection   | 20 (11.5%)            | 5 (8.9%)  |
| Arthralgia                | 17 (9.8%)             | 2 (3.6%)  |
| Infusion related reaction | 16 (9.2%)             | 6 (10.7%) |

| Dictionary Derived Term           | INEBILIZUMAB 300mg IV | Placebo     |
|-----------------------------------|-----------------------|-------------|
| Nasopharyngitis                   | 13 (7.5%)             | 6 (10.7%)   |
| Headache                          | 13 (7.5%)             | 4 (7.1%)    |
| Back pain                         | 13 (7.5%)             | 2 (3.6%)    |
| Fall                              | 8 (4.6%)              | 1 (1.8%)    |
| Diarrhoea                         | 8 (4.6%)              | 3 (5.4%)    |
| Hypoaesthesia                     | 6 (3.4%)              | 1 (1.8%)    |
| Nausea                            | 6 (3.4%)              | 3 (5.4%)    |
| Cystitis                          | 5 (2.9%)              | 0 (0.0%)    |
| Anaemia                           | 5 (2.9%)              | 2 (3.6%)    |
| Eye pain                          | 5 (2.9%)              | 1 (1.8%)    |
| Upper respiratory tract infection | 5 (2.9%)              | 3 (5.4%)    |
| Oropharyngeal pain                | 4 (2.3%)              | 1 (1.8%)    |
| Paraesthesia                      | 4 (2.3%)              | 0 (0.0%)    |
| Rash                              | 4 (2.3%)              | 0 (0.0%)    |
| Dizziness                         | 4 (2.3%)              | 1 (1.8%)    |
| Insomnia                          | 4 (2.3%)              | 1 (1.8%)    |
| Depression                        | 4 (2.3%)              | 5 (8.9%)    |
| Neutropenia                       | 4 (2.3%)              | 0 (0.0%)    |
| Neck pain                         | 4 (2.3%)              | 1 (1.8%)    |
| Influenza                         | 4 (2.3%)              | 2 (3.6%)    |
| Subjects(filtered)                | 125 (71.8%)           | 41 (73.2%)  |
| 1stCollItemSubjects               | 174 (100.0%)          | 56 (100.0%) |

Source: JRevselADSLASTRFL\_Y AEDECODbyTRT01AfilTRTEMFL\_YandEPOCH\_RCTdescbyMEDI551

**Table 50: Treatment Emergent Adverse Events during RCP, Preferred Term, >2% of inebilizumab population, (greater than placebo shaded), anti-AQP4 IgG seropositive**

| Dictionary Derived Term           | MEDI-551 300mg IV | Placebo   |
|-----------------------------------|-------------------|-----------|
| Urinary tract infection           | 18 (11.2%)        | 5 (9.6%)  |
| Headache                          | 16 (9.9%)         | 4 (7.7%)  |
| Arthralgia                        | 16 (9.9%)         | 2 (3.8%)  |
| Infusion related reaction         | 15 (9.3%)         | 5 (9.6%)  |
| Nasopharyngitis                   | 12 (7.5%)         | 6 (11.5%) |
| Nausea                            | 11 (6.8%)         | 3 (5.8%)  |
| Back pain                         | 11 (6.8%)         | 2 (3.8%)  |
| Diarrhoea                         | 7 (4.3%)          | 3 (5.8%)  |
| Fall                              | 7 (4.3%)          | 1 (1.9%)  |
| Upper respiratory tract infection | 5 (3.1%)          | 3 (5.8%)  |
| Anaemia                           | 5 (3.1%)          | 2 (3.8%)  |
| Hypoaesthesia                     | 5 (3.1%)          | 1 (1.9%)  |
| Eye pain                          | 5 (3.1%)          | 1 (1.9%)  |
| Rash                              | 5 (3.1%)          | 0 (0.0%)  |
| Depression                        | 4 (2.5%)          | 5 (9.6%)  |
| Hypertension                      | 4 (2.5%)          | 2 (3.8%)  |
| Influenza                         | 4 (2.5%)          | 2 (3.8%)  |

| Dictionary Derived Term | MEDI-551 300mg IV | Placebo     |
|-------------------------|-------------------|-------------|
| Neck pain               | 4 (2.5%)          | 1 (1.9%)    |
| Oropharyngeal pain      | 4 (2.5%)          | 1 (1.9%)    |
| Dizziness               | 4 (2.5%)          | 1 (1.9%)    |
| Cystitis                | 4 (2.5%)          | 0 (0.0%)    |
| Neutropenia             | 4 (2.5%)          | 0 (0.0%)    |
| Paraesthesia            | 4 (2.5%)          | 0 (0.0%)    |
| Subjects(filtered)      | 118 (73.3%)       | 37 (71.2%)  |
| 1stCollItemSubjects     | 161 (100.0%)      | 52 (100.0%) |

Source: JRevSelADSL\_ASTRFL\_Y STRATA\_SEROPOS AEDECODbyADSLTRT01AfiltRTEMFL\_Y EPOCH\_RCP

**Table 51: Treatment emergent adverse events during RCP, by SOC, Safety population**

| Body System or Organ Class                                          | Inebilizumab<br>300mg IV | Placebo     |
|---------------------------------------------------------------------|--------------------------|-------------|
| Infections and infestations                                         | 66 (37.9%)               | 23 (41.1%)  |
| Musculoskeletal and connective tissue disorders                     | 38 (21.8%)               | 12 (21.4%)  |
| Nervous system disorders                                            | 35 (20.1%)               | 13 (23.2%)  |
| Gastrointestinal disorders                                          | 30 (17.2%)               | 13 (23.2%)  |
| Injury, poisoning and procedural complications                      | 27 (15.5%)               | 11 (19.6%)  |
| Skin and subcutaneous tissue disorders                              | 24 (13.8%)               | 10 (17.9%)  |
| General disorders and administration site conditions                | 22 (12.6%)               | 6 (10.7%)   |
| Psychiatric disorders                                               | 12 (6.9%)                | 8 (14.3%)   |
| Investigations                                                      | 13 (7.5%)                | 6 (10.7%)   |
| Respiratory, thoracic and mediastinal disorders                     | 13 (7.5%)                | 4 (7.1%)    |
| Eye disorders                                                       | 10 (5.7%)                | 7 (12.5%)   |
| Blood and lymphatic system disorders                                | 12 (6.9%)                | 4 (7.1%)    |
| Vascular disorders                                                  | 7 (4.0%)                 | 7 (12.5%)   |
| Metabolism and nutrition disorders                                  | 4 (2.3%)                 | 4 (7.1%)    |
| Reproductive system and breast disorders                            | 4 (2.3%)                 | 2 (3.6%)    |
| Renal and urinary disorders                                         | 5 (2.9%)                 | 1 (1.8%)    |
| Hepatobiliary disorders                                             | 4 (2.3%)                 | 1 (1.8%)    |
| Ear and labyrinth disorders                                         | 4 (2.3%)                 | 1 (1.8%)    |
| Cardiac disorders                                                   | 1 (0.6%)                 | 3 (5.4%)    |
| Endocrine disorders                                                 | 3 (1.7%)                 | 0 (0.0%)    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (1.1%)                 | 0 (0.0%)    |
| Immune system disorders                                             | 2 (1.1%)                 | 0 (0.0%)    |
| Surgical and medical procedures                                     | 1 (0.6%)                 | 0 (0.0%)    |
| Subjects(filtered)                                                  | 125 (71.8%)              | 41 (73.2%)  |
| 1stCollItemSubjects                                                 | 174 (100.0%)             | 56 (100.0%) |

Source: JRevSelASTRFL\_Y SOCbyADSLTRT01AfiltANL01FL\_Y

**Table 52: Treatment emergent adverse events during the RCP, by SOC, anti-AQP4 IgG seropositive population**

| Body System or Organ Class                                          | MEDI-551 300mg IV | Placebo     |
|---------------------------------------------------------------------|-------------------|-------------|
| Infections and infestations                                         | 63 (39.1%)        | 23 (44.2%)  |
| Nervous system disorders                                            | 36 (22.4%)        | 14 (26.9%)  |
| Musculoskeletal and connective tissue disorders                     | 36 (22.4%)        | 11 (21.2%)  |
| Gastrointestinal disorders                                          | 29 (18.0%)        | 12 (23.1%)  |
| Injury, poisoning and procedural complications                      | 26 (16.1%)        | 10 (19.2%)  |
| Skin and subcutaneous tissue disorders                              | 24 (14.9%)        | 10 (19.2%)  |
| General disorders and administration site conditions                | 21 (13.0%)        | 5 (9.6%)    |
| Psychiatric disorders                                               | 11 (6.8%)         | 7 (13.5%)   |
| Respiratory, thoracic and mediastinal disorders                     | 13 (8.1%)         | 4 (7.7%)    |
| Investigations                                                      | 12 (7.5%)         | 5 (9.6%)    |
| Eye disorders                                                       | 9 (5.6%)          | 7 (13.5%)   |
| Blood and lymphatic system disorders                                | 12 (7.5%)         | 3 (5.8%)    |
| Vascular disorders                                                  | 7 (4.3%)          | 6 (11.5%)   |
| Metabolism and nutrition disorders                                  | 3 (1.9%)          | 4 (7.7%)    |
| Reproductive system and breast disorders                            | 4 (2.5%)          | 2 (3.8%)    |
| Ear and labyrinth disorders                                         | 4 (2.5%)          | 1 (1.9%)    |
| Hepatobiliary disorders                                             | 4 (2.5%)          | 1 (1.9%)    |
| Renal and urinary disorders                                         | 4 (2.5%)          | 1 (1.9%)    |
| Cardiac disorders                                                   | 1 (0.6%)          | 3 (5.8%)    |
| Endocrine disorders                                                 | 2 (1.2%)          | 0 (0.0%)    |
| Immune system disorders                                             | 1 (0.6%)          | 0 (0.0%)    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.6%)          | 0 (0.0%)    |
| Subjects(filtered)                                                  | 118 (73.3%)       | 37 (71.2%)  |
| 1stCollItemSubjects                                                 | 161 (100.0%)      | 52 (100.0%) |

Source: JRevSelADSLASTRTFL\_Y STRATA\_SEROPOS SOCbyADSLTRT01AfilTRTEMFL\_Y EPOCH\_RCP

## MedDRA SMQs

### Haematopoietic cytopenias

AEs that occurred during the RCP and that are included in the Broad SMQ, Haematopoietic cytopenias (SMQ), are shown in (Table 53). None were considered serious. All occurred in seropositive subjects. Two subjects had 2 AEs (neutropenia and anemia; anemia and red blood cell count decreased) and one subject had 3 AEs (Leukopenia, Lymphopenia, Neutropenia). A decrease in a white cell count occurred in 10 of 174 subjects treated with inebilizumab (5.8%) and in no subjects in the placebo group.

**Table 53: Adverse events, Haematopoietic cytopenias SMQ, safety population**

| AEDECOD                    | MEDI-551 (N=161)        |      | Placebo (N=52)          |      |
|----------------------------|-------------------------|------|-------------------------|------|
|                            | AQP4-IgG seropositive** |      | AQP4-IgG seropositive** |      |
|                            | N*                      | %    | N*                      | %    |
| Anaemia                    | 6                       | 3.73 | 2                       | 3.85 |
| Leukopenia                 | 1                       | 0.62 | 0                       | 0    |
| Lymphocyte count decreased | 2                       | 1.24 | 0                       | 0    |
| Lymphopenia                | 3                       | 1.86 | 0                       | 0    |
| Neutropenia                | 4                       | 2.48 | 0                       | 0    |

**Source:** SMQNAME\_Hematopoietic Cytopenias Subset of ANL01FL\_Y Subset of ASTRFL\_Y Subset of SMQ\_MAED By (USUBJID, STRATA, TRT01A, AEDECOD) NUSUBJIDbySTRATAbyTRT01A By (AEDECOD).jmp

\*N: NUSUBJID

\*\* : there were no seronegative subjects

The mean study day start of the AE's above that involved white blood cells was study day 45±38 and the end study day was 303±351.

*Reviewer Comment: 2 additional AEs of Neutropenia occurred in inebilizumab subjects initially treated with placebo, one in the open label treatment period and one in the safety follow-up period.*

#### Drug related Hepatic disorders – comprehensive

The occurrence of events included in the broad SMQ for drug-related hepatic disorders was similar for the two treatment groups and most involved elevated transaminases ([Table 54](#)). However, there was one subject treated with inebilizumab (USUBJID: CD-IA-MEDI-551-1155/ (b) (6)) of “hepatic function abnormal” that resulted in discontinuation of the study drug. The full narrative for this subject is in [13.8](#).

**Table 54: Adverse events, drug related hepatic disorders SMQ, anti-AQP4 IgG safety population**

| AEDECOD                              | Seropositive** |      |                  |      |                |      |
|--------------------------------------|----------------|------|------------------|------|----------------|------|
|                                      | Total (N=213)  |      | MEDI-555 (N=161) |      | Placebo (N=52) |      |
|                                      | N*             | %    | N*               | %    | N*             | %    |
| Alanine aminotransferase increased   | 3              | 1.41 | 2                | 1.24 | 1              | 1.92 |
| Aspartate aminotransferase increased | 1              | 0.47 | 0                | 0    | 1              | 1.92 |
| Blood bilirubin increased            | 1              | 0.47 | 0                | 0    | 1              | 1.92 |
| Gamma-glutamyltransferase increased  | 3              | 1.41 | 2                | 1.24 | 1              | 1.92 |
| Hepatic enzyme increased             | 1              | 0.47 | 0                | 0    | 1              | 1.92 |
| Hepatic function abnormal            | 2              | 0.94 | 2                | 1.24 | 0              | 0    |
| Hepatic steatosis                    | 1              | 0.47 | 1                | 0.62 | 0              | 0    |
| Hepatitis                            | 1              | 0.47 | 0                | 0    | 1              | 1.92 |
| Hypoalbuminaemia                     | 1              | 0.47 | 0                | 0    | 1              | 1.92 |
| Liver function test increased        | 1              | 0.47 | 1                | 0.62 | 0              | 0    |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

**Source:** SMQNAME\_Drug Related Hepatic Comp Subset of ANL01FL\_Y Subset of ASTRFL\_Y Subset of SMQ\_MAE By (USUBJID, STRATA, TRT01A, AEDECOD) NUSUBJIDbyTRT01AbySTRATA By (AEDECOD).jmp

\*: N = NUSUBJID

\*\*: there were no Seronegative subjects

#### ODE1 Adverse Event groupings

Adverse events during the RCP were categorized using the ODE1 grouping of preferred terms ([Table 55](#)). Arthralgia, arthritis and arthrosis was more common in subjects treated with inebilizumab, in agreement with the standard analysis of preferred terms ([Table 49](#)).

**Table 55: ODE1 Adverse Event Groups by Treatment Group, 5% of more of the inebilizumab group, safety population**

| Analysis Columns                                                        | INEBILIZUMAB 300mg IV |       | Placebo |       |
|-------------------------------------------------------------------------|-----------------------|-------|---------|-------|
| infection, all                                                          | 64                    | 36.8% | 23      | 41.1% |
| URI, cold, rhinitis, upper resp tract infection, flu-like illness       | 32                    | 18.4% | 11      | 19.6% |
| UTI                                                                     | 26                    | 14.9% | 6       | 10.7% |
| headache                                                                | 22                    | 12.6% | 6       | 10.7% |
| arthralgia, arthritis, arthrosis                                        | 18                    | 10.3% | 2       | 3.6%  |
| allergic RXN, hypersensitivity                                          | 16                    | 9.2%  | 7       | 12.5% |
| infection, viral                                                        | 15                    | 8.6%  | 7       | 12.5% |
| dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis    | 13                    | 7.5%  | 9       | 16.1% |
| fall, dizziness, balance disorder                                       | 13                    | 7.5%  | 2       | 3.6%  |
| fall, dizziness, balance disorder, gait disturbance, difficulty walking | 13                    | 7.5%  | 2       | 3.6%  |
| Nausea, vomiting                                                        | 12                    | 6.9%  | 8       | 14.3% |
| diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff        | 11                    | 6.3%  | 4       | 7.1%  |
| eye other                                                               | 11                    | 6.3%  | 5       | 8.9%  |

**Source:** Final Table ODE1 AN01FL\_Y

### 8.4.6. Laboratory Findings

#### Hematology

##### Red blood cells

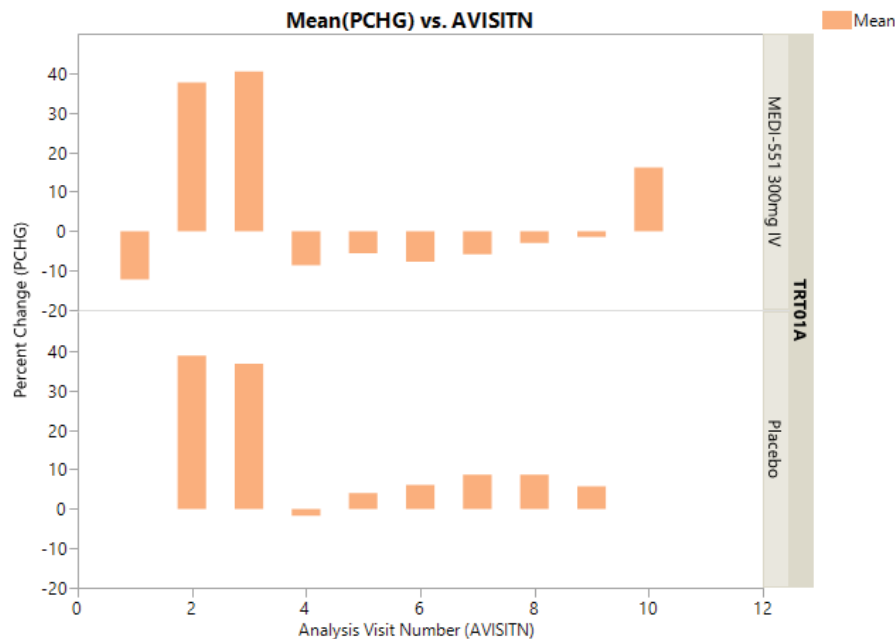
There were no significant alterations in the RBC count, hemoglobin level or hematocrit during treatment with inebilizumab compared to the placebo group. One subject ( (b) (6) ) being treated with inebilizumab had a significant decrease in all red blood cell measures that appears attributable to menorrhagia.

##### White blood cells

##### Leukocytes

During the RCP, the overall leukocyte count increased in both treatment groups at visits 3 (Study day 15) and 4 (Study day 29) and returned to just above baseline in the subjects treated with placebo but to below baseline for those treated with inebilizumab (Figure 6).

**Figure 6: Percent change from baseline, leukocyte count, by analysis visit, by actual treatment, RCP, safety population**



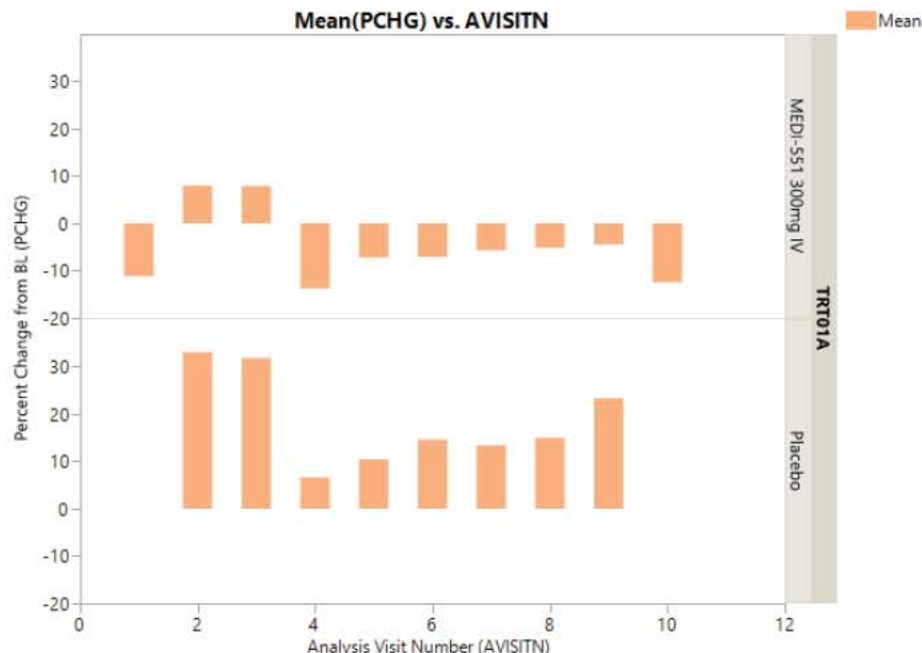
**Source:** EPOCH\_RCP Subset of PARAM\_Leukocytes Subset of LBCAT\_HEME Subset of ADLB.jmp

*Reviewer Comment: The elevation within the first month may, in part, be attributable to the corticosteroids administered as pre-treatment and for the first 21 days of treatment (see 6.1.1, "Treatment", page 25 of the review). Any percent decrease from baseline in leukocyte count was relatively minor; no change was greater than 3% in either treatment group. The lowest leukocyte count during the RCP was  $2.1 \times 10^3/\mu\text{L}$  in the inebilizumab group and  $2.88 \times 10^3/\mu\text{L}$  in the placebo group.*

#### Lymphocytes

The lymphocyte count also increased within the first 4 weeks after the initial infusion and then decreased below baseline in subjects treated with inebilizumab but returned to just above baseline in the placebo group (Figure 7).

**Figure 7: Percent change from baseline, lymphocyte count, by analysis visit, by actual treatment, RCP, as treated population**



Source: EPOCH\_RCP Subset of PARAM\_LYMPHS Subset of LBCAT\_HEME Subset of ADLB.jmp

*Reviewer Comment: The sponsor reported 10 adverse events in the special interest category of "cytopenias", all in subjects being treated with inebilizumab. None were considered serious and all resolved without a change in the inebilizumab.*

At the time of the 120-day safety update the reduction in lymphocytes remained relatively stable over the course of treatment (Table 56).

**Table 56: Reduction in lymphocytes count by visit, any inebilizumab population, 120-day safety update**

| AVISIT     | Percent change from baseline |      |         |        |
|------------|------------------------------|------|---------|--------|
|            | N Rows                       | Mean | Std Dev | Median |
| Week 1     | 215                          | 14   | 58.1    | 4.4    |
| Week 2     | 217                          | 13.7 | 52.4    | 4.86   |
| Week 4     | 214                          | -8.7 | 34      | -16    |
| Week 8     | 217                          | -2.8 | 35.4    | -7.4   |
| Week 12    | 180                          | -1.8 | 33.5    | -6.7   |
| Week 16    | 184                          | 0.07 | 39.3    | -3.8   |
| Week 22    | 172                          | -0.9 | 34.4    | -8.6   |
| Week 28    | 146                          | 0.71 | 35.4    | -4.3   |
| Week 0 OLP | 86                           | 6.47 | 48.3    | -4     |

| AVISIT       | Percent change from baseline |      |         |        |
|--------------|------------------------------|------|---------|--------|
|              | N Rows                       | Mean | Std Dev | Median |
| Week 2 OLP   | 213                          | -3.7 | 34.8    | -10    |
| Week 4 OLP   | 215                          | -6.5 | 31      | -10    |
| Week 13 OLP  | 227                          | -7   | 29.6    | -9.8   |
| Week 26 OLP  | 230                          | -1.3 | 31.8    | -4.5   |
| Week 39 OLP  | 175                          | -0.6 | 33.1    | -5.3   |
| Week 52 OLP  | 164                          | 3.47 | 37.2    | -0.7   |
| Week 65 OLP  | 136                          | 5.32 | 37.6    | 0.56   |
| Week 78 OLP  | 123                          | 2.37 | 34.5    | -4.2   |
| Week 91 OLP  | 114                          | 3.05 | 36.5    | -1     |
| Week 104 OLP | 100                          | 4.72 | 38.5    | 2.09   |
| Week 117 OLP | 86                           | 8.59 | 42.3    | 3.01   |
| Week 78 OLP  | 62                           | 4.58 | 42.2    | -4.1   |
| Week 143 OLP | 44                           | 10.6 | 44.7    | 0.57   |
| Week 156 OLP | 30                           | 5.73 | 41.7    | 0.3    |
| Week 169 OLP | 18                           | 4.93 | 37.7    | -1.7   |
| Week 182 OLP | 14                           | 7.79 | 42.3    | -1.1   |

Source: LBTEST\_LYMPHS Subset of LBCAT\_HEMATOL ubset of ANYMDFL\_Y Subset of ADLB 120 day updatePCHG By (AVISITN).jmp

### CD19+ cells

CD19+ cell counts did not differ by treatment group at baseline ([Table 57](#)).

**Table 57: CD19+ cells at baseline, mITT**

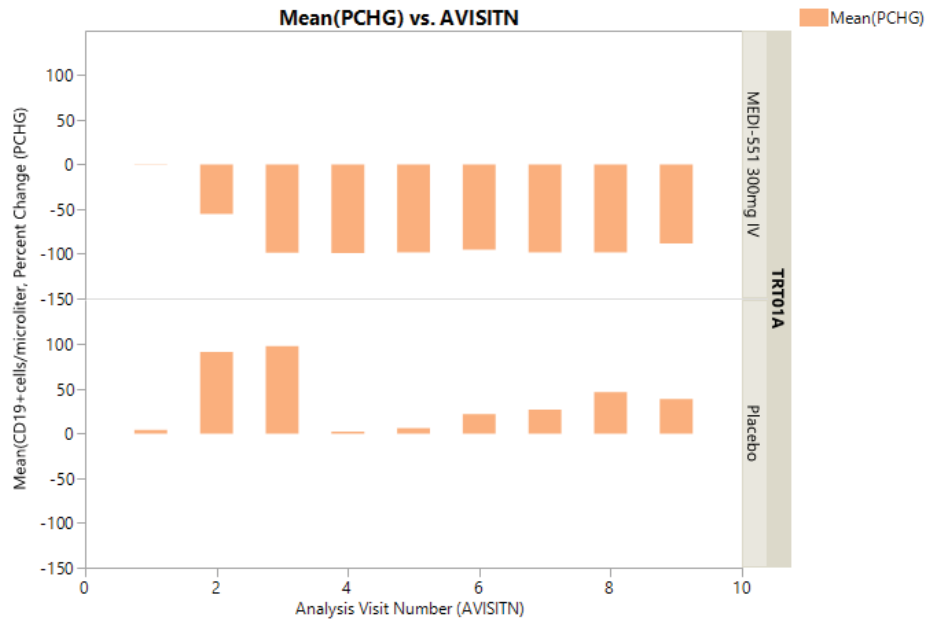
| TRT01A            | AVAL |        |         |        |        |        |           |
|-------------------|------|--------|---------|--------|--------|--------|-----------|
|                   | N    | Mean   | Std Dev | Min    | Max    | Median | N Missing |
| MEDI-551 300mg IV | 173  | 213.95 | 149.56  | 0.1*   | 1146   | 183.84 | 0         |
| Placebo           | 56   | 218.72 | 271.76  | 14.145 | 2013.9 | 160.31 | 0         |

Source: ABLFL\_Y Subset of PARAM\_CD19 Subset of ADLBFC AVAL By (TRT01A).jmp

\*: subject (b) (6) had a baseline count below the limit of quantitation

For subjects treated with inebilizumab, CD19 positive cells decreased immediately after treatment and remained below baseline for the duration of the RCP. There was an increase in CD19+ cells for the first few weeks in the placebo group followed by a return to baseline ([Figure 8](#)).

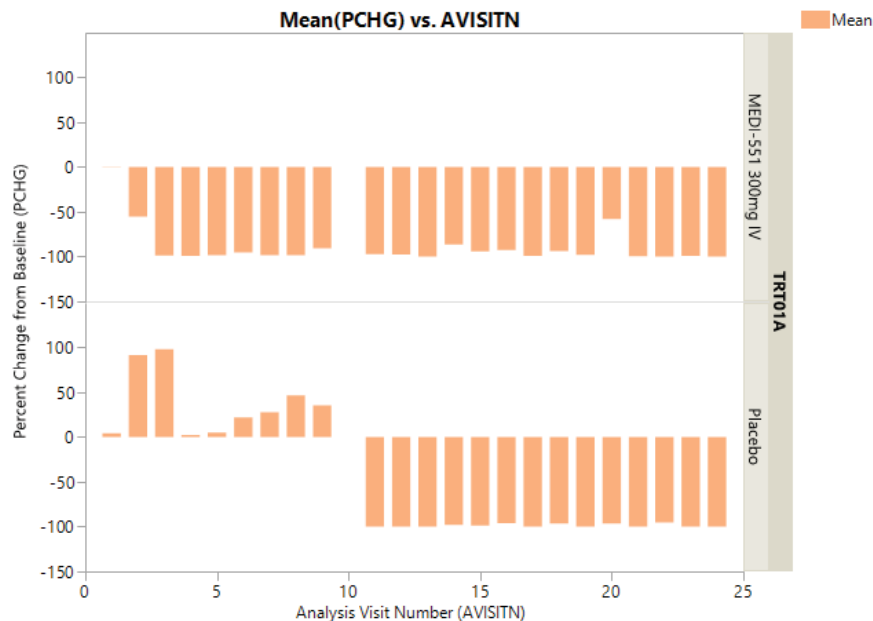
**Figure 8: CD19+ cells, mean percent change from baseline by visit, RCP, safety population**



Source: LBTEST\_CD19 Subset of EPOCH\_RCP Subset of ADLBFC.jmp

From the onset of treatment with inebilizumab in the OLP, the mean CD19+ cell count was reduced in both treatment groups for the duration of treatment ([Figure 9](#)).

**Figure 9: Mean CD19+ cell count by visit, mITT**



Source: PARAM\_CD19 Subset of EPOCH\_RCPandOLP Subset of ADLBFC.jmp

Exclude (b) (6): MEDI-551 subject with 100% and 153,110% increase at Week 13 OLP visit (Day 92 OLP ADY 288); Baseline CD19 count was below the limit of detection.

**Reviewer Comment:** *Treatment with inebilizumab resulted in a reduction in CD19+ cells to below the level of quantitation regardless of age, sex, ethnic group or AQP4-IgG status.*

CD19+ cell count at the time of an attack

The distribution of the percent change from baseline in the CD19+ cell count for each treatment group at the time of an attack visit during the RCP is shown in [Figure 10](#). The mean and median percent change CD19+ count at the time of an attack is shown in [Table 58](#). The absolute CD19+ cell count by visit type, including attack visits, is shown in [Table 59](#).

**Figure 10: Distribution of percent change from baseline in CD19+ cell count at attack visit**

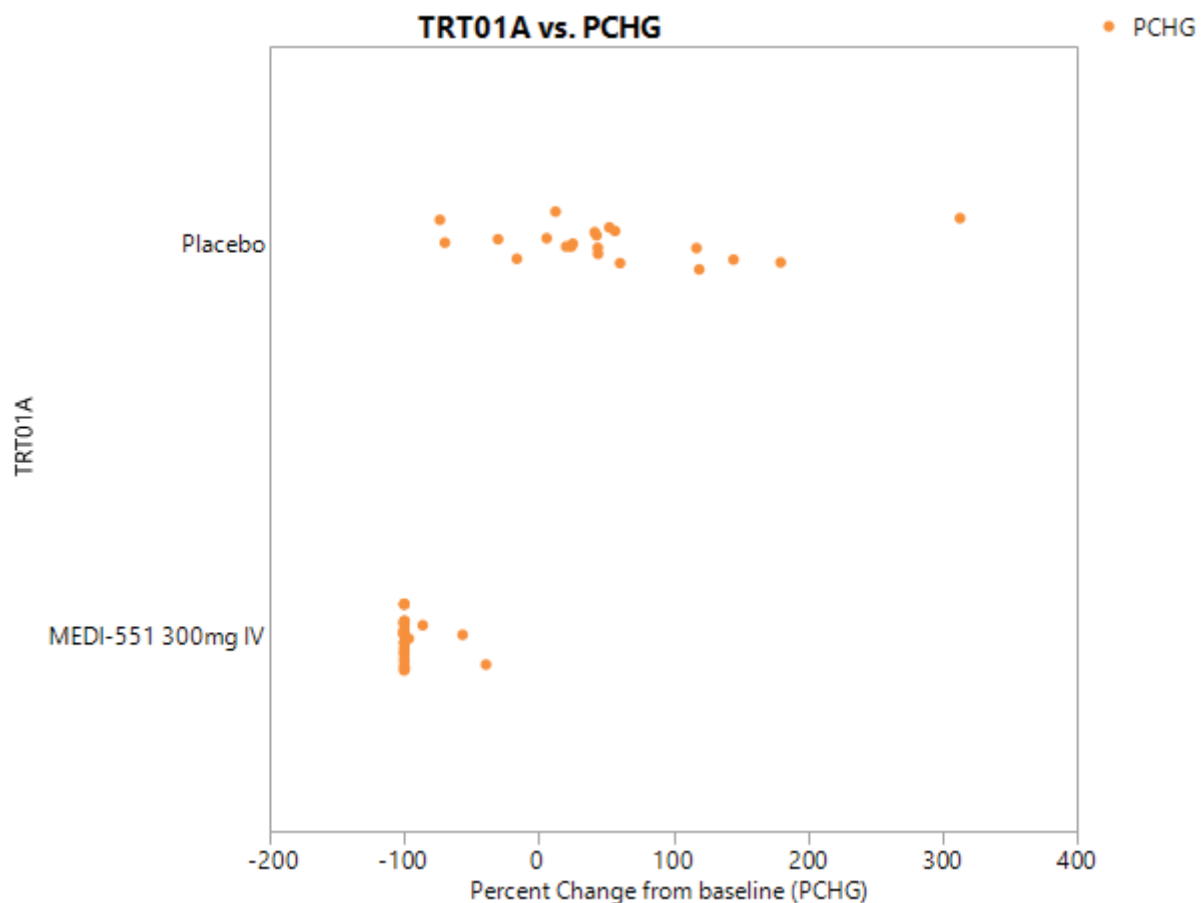


**Table 58: Percent change from baseline in CD19+ cell count at an attack visit**

| TRT01A            | Percent change from baseline |      |         |        |
|-------------------|------------------------------|------|---------|--------|
|                   | N                            | Mean | Std Dev | Median |
| MEDI-551 300mg IV | 36                           | -96  | 12.4    | -100   |
| Placebo           | 21                           | 53.1 | 86.7    | 43     |

**Source:** EPOCH\_RCP Subset of VISIT\_ATTACK Subset of ANYMDFL\_Y Subset of PARAM\_CD19 Subset of ADLBFC PCHG By (TRT01A).jmp

**Table 59: CD19+ cell count by visit, treatment group and censor for unanimous AC-confirmed attack**

| VISITNUM | TRT01A            | N Rows | Mean (AVAL)        |        | Median (AVAL)   |        |
|----------|-------------------|--------|--------------------|--------|-----------------|--------|
|          |                   |        | Censor from TTE*** |        | Censor from TTE |        |
|          |                   |        | 0                  | 1      | 0               | 1      |
| 2*       | MEDI-551 300mg IV | 147    | 164.89             | 209.57 | 140.7           | 184.54 |
| 2        | Placebo           | 49     | 200.15             | 183.78 | 142.33          | 158.59 |
| 3        | MEDI-551 300mg IV | 158    | 0.2282             | 95.536 | 0.1             | 0.1    |
| 3        | Placebo           | 46     | 271.63             | 419.71 | 150.76          | 287.39 |
| 4        | MEDI-551 300mg IV | 154    | 0.2077             | 2.2582 | 0.1             | 0.1    |
| 4        | Placebo           | 49     | 303.67             | 442.81 | 255.99          | 278.77 |
| 5        | MEDI-551 300mg IV | 147    | 0.177              | 0.1954 | 0.1             | 0.1    |
| 5        | Placebo           | 47     | 151.59             | 153.89 | 114.58          | 127.81 |
| 6        | MEDI-551 300mg IV | 141    | 0.2315             | 0.2174 | 0.1             | 0.1    |
| 6        | Placebo           | 41     | 235.26             | 171.12 | 128.52          | 149.11 |
| 7        | MEDI-551 300mg IV | 127    | 0.199              | 3.1901 | 0.1505          | 0.1    |
| 7        | Placebo           | 37     | 255.46             | 239.57 | 178.04          | 158.87 |
| 8        | MEDI-551 300mg IV | 124    | 0.1                | 0.2104 | 0.1             | 0.1    |
| 8        | Placebo           | 36     | 188.33             | 250.58 | 131.96          | 167.45 |
| 9        | MEDI-551 300mg IV | 118    | 0.1                | 2.0977 | 0.1             | 0.1    |
| 9        | Placebo           | 27     | 444.92             | 230.62 | 444.92          | 190.07 |
| 10       | MEDI-551 300mg IV | 82     |                    | 21.037 |                 | 0.1    |
| 10       | Placebo           | 17     |                    | 322.17 |                 | 256.35 |
| 97**     | MEDI-551 300mg IV | 36     | 1.3255             | 19.299 | 0.1             | 0.1    |
| 97       | Placebo           | 26     | 263.25             | 182.6  | 192.08          | 206.31 |
| 98       | MEDI-551 300mg IV | 9      | 3.7922             | 0.1347 | 0.1655          | 0.1    |
| 98       | Placebo           | 10     | 187.76             | 874.15 | 194.51          | 146.99 |

**Source:** EPOCH\_RCP Subset of Join PARAM\_TTAAUN subset ADTTE c PARAM\_CD19 subset ADLBFC AVAL By (VISITNUM, TRT01A).jmp

\*: Visit number 2 to 10 represent days 1 through 197/Early discontinuation visits

\*\* : Visit 97 is an attack visit; Visit 98 is an attack follow-up visit

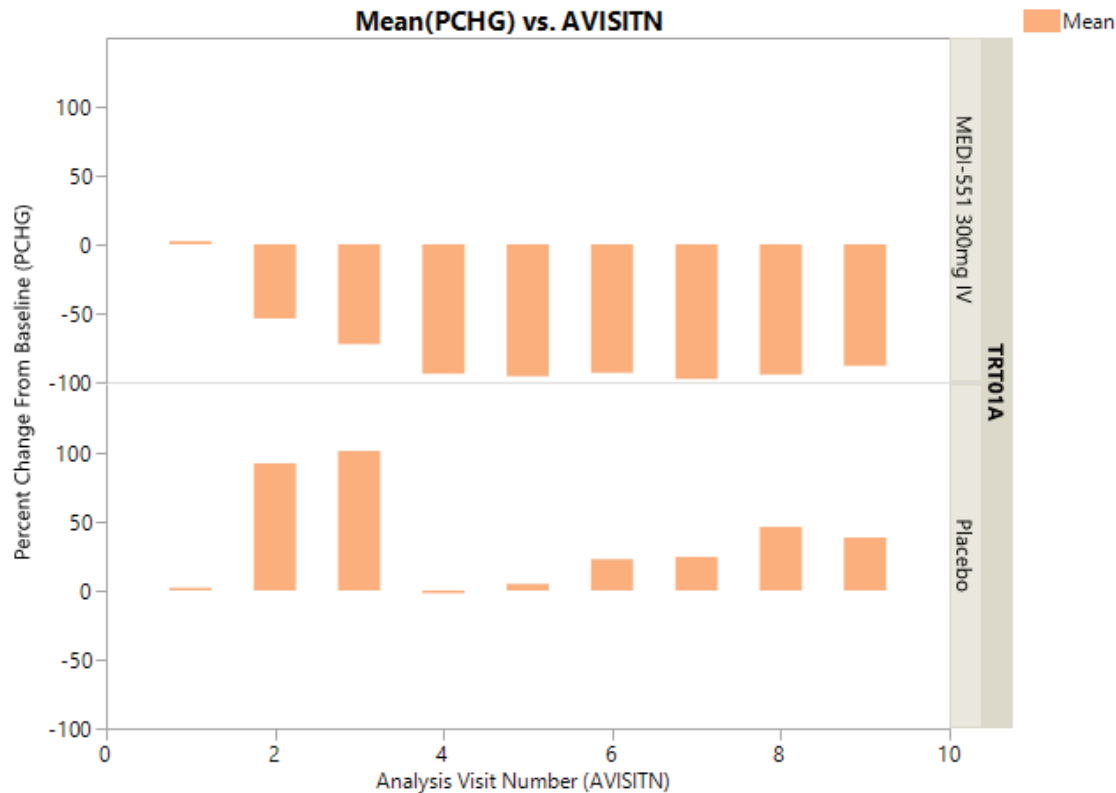
\*\*\*: CNSR of 0 indicates not censored, i.e. did have an attack

*Reviewer Comment: There is no indication that attacks in the inebilizumab group were related to failure to adequately suppress CD19+ cells.*

#### CD20+ cells

The changes in CD20+ cells during the RCP were comparable to those for CD19+ cells ([Figure 11](#)).

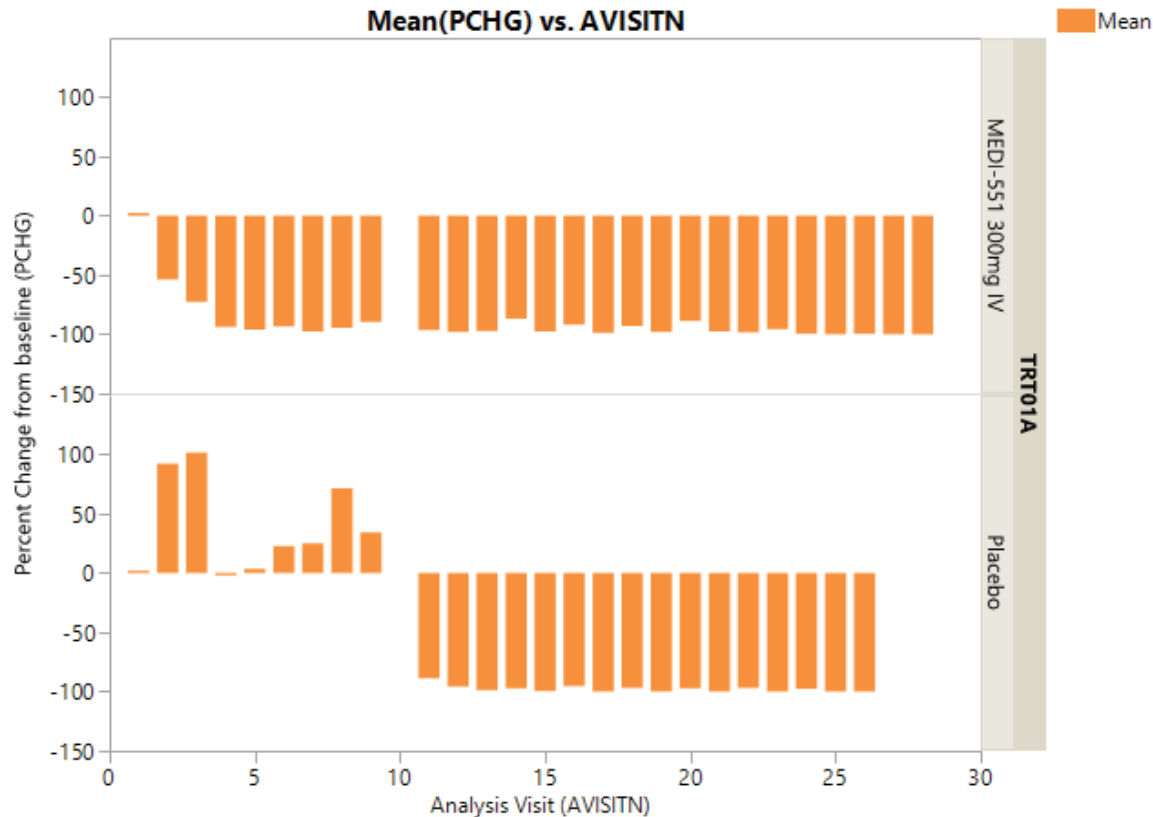
**Figure 11: CD20+ cells, percent change from baseline by visit, RCP, as treated population**



Source: CD20 Subset of EPOCH\_RCP Subset of ADLBFC.jmp

With the onset of the open label treatment phase, subjects treated with placebo during the RCP showed the same reduction as those treated with inebilizumab during the RCP ([Figure 12](#)).

**Figure 12: Percent reduction in CD20+ cells be visit and RCP treatment group**



Source: PARAM\_CD20 Subset of ADLBFC.jmp

### Platelets

Platelet counts remained stable throughout the RCP.

### Chemistry

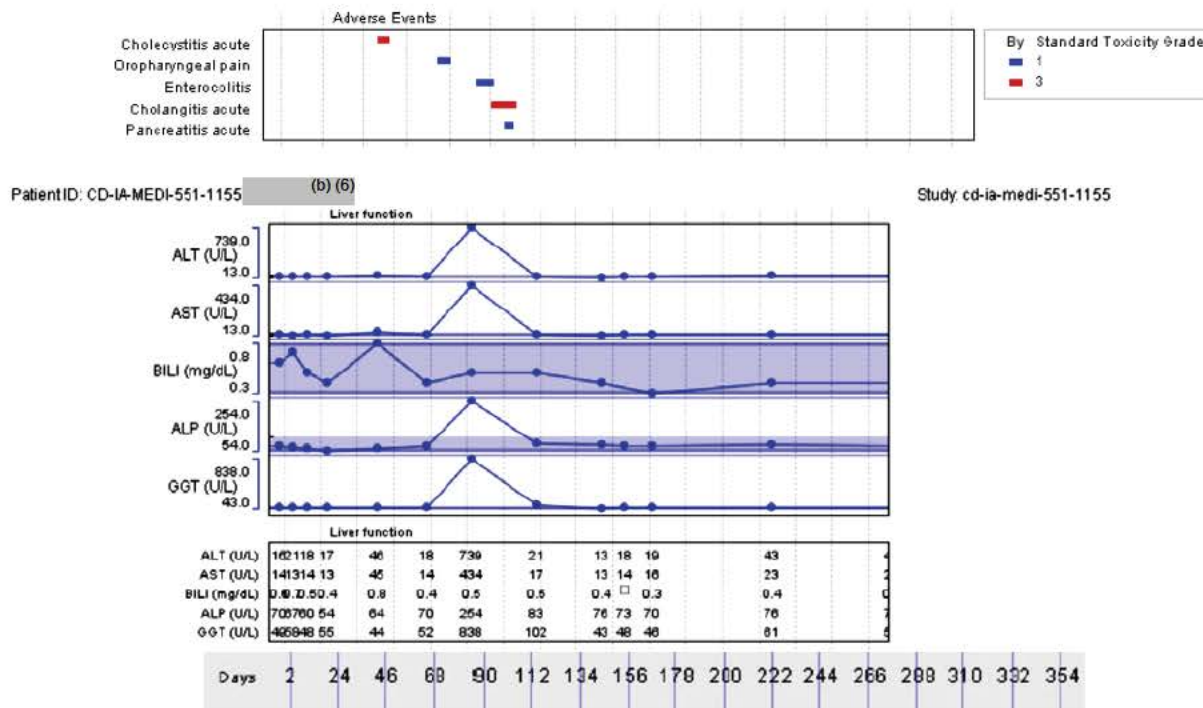
### Transaminases

Any shift in ALT from a baseline of normal to high during the RCP was seen in 21.3% of subjects treated with inebilizumab and in 26.8% of subjects treated with placebo. Any shift of AST from normal to high was seen in 15.5% of subjects treated with inebilizumab and in 23.2% of subjects treated with placebo. Six subjects had an ALT more the 3 times the Upper Limit of Normal (ULN), 5 treated with inebilizumab and one with placebo. One subject treated with placebo (Subject (b) (6)) had an elevation of ALT more than 3 times the ULN but AST was not above 3 times ULN. The event corresponded to a non-serious AE of “non-specific reactive hepatitis” that resolved spontaneously. None of the other ALT elevations more than 3 times

ULN corresponded to an AE. Seven subjects had an elevation of AST more than 3 times the ULN, 5 treated with inebilizumab and 2 with placebo. None corresponded to an AE. The only subject with an elevation of both ALT and AST more than 5 times ULN is described below. There were no Hy's Law cases

One subject (b) (6) treated with inebilizumab during the RCP had an elevation of ALT and AST over 5 times the ULN at approximately study day 90. Bilirubin was not elevated. There was a past history of fatty liver. Oxcarbazepine was a concurrent medication. There had been an attack of cholecystitis at about day 55 that resulted in a cholecystectomy. A few days earlier this subject had an AE of enteritis that resolved. Within a week after that illness the transaminases were found to be elevated but the subject was asymptomatic at that time. Within a week, however, the subject was diagnosed with acute cholangitis and was treated with antibiotics and a biliary drainage tube was placed. The transaminases returned to normal soon thereafter. The Graphic Patient Profile for this subject is in [Figure 13](#).

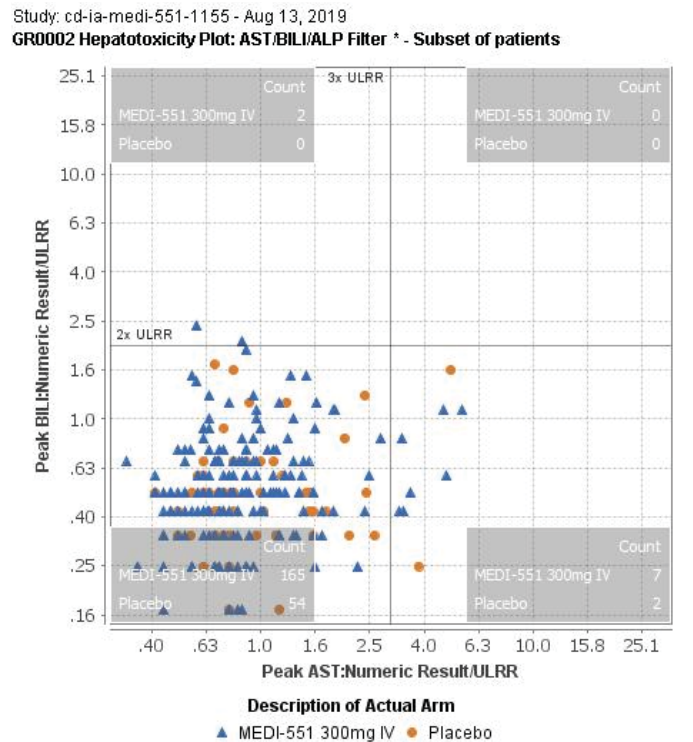
Figure 13: Graphic Patient Profile, Subject (b) (6)



### Hy's Law

There were no Hy's Law subjects. There were no instances of a BILI > 2X ULN. The plot of AST elevations by bilirubin elevation is shown in Figure 14.

**Figure 14: Hy's Law hepatotoxicity plot**



Patient Selection Criteria: ADSL Subject Level Dataset.As Treated Population Flag ...  
Output Filter: ALP:Numeric Result < 2x ALP:ULN

Page 1 of 1

Source: JRevSelASTRFL\_Y BILI BLbyMAX CHG by ARM Scatter Plot

#### Renal Function

There were no significant alterations in renal function during the RCP

#### Electrolytes

A shift from normal to low potassium occurred during the RCP in 18 subjects (10.3%) treated with inebilizumab and in 4 subjects (7.1%) treated with placebo. There was one AE of hypokalemia during the RCP.

#### Immunoglobulins

For those treated with inebilizumab, there was a relatively small reduction of 10% in total immunoglobulins at week 28 of the RCP. The largest reduction in the individual Ig classes was

for IgM and IgE. There were no reductions in any immunoglobulin class for those treated with placebo ([Table 60](#)).

**Table 60: Percent change from baseline in immunoglobulins at week 28 of the RCP**

| Parameter | TRT01A            | N Rows | Percent Change from Baseline |         |     |      |        |
|-----------|-------------------|--------|------------------------------|---------|-----|------|--------|
|           |                   |        | Mean                         | Std Dev | Min | Max  | Median |
| Total     | MEDI-551 300mg IV | 93     | -8.8                         | 16.4    | -70 | 39.1 | -9.9   |
|           | Placebo           | 25     | 5.75                         | 29.5    | -76 | 60.7 | 11.4   |
| IgG       | MEDI-551 300mg IV | 93     | -3.9                         | 19.2    | -68 | 59.1 | -6.3   |
|           | Placebo           | 25     | 7.85                         | 32.4    | -76 | 69.7 | 9.51   |
| IgM       | MEDI-551 300mg IV | 93     | -34                          | 21.9    | -95 | 51.6 | -33    |
|           | Placebo           | 25     | 8                            | 46.8    | -77 | 146  | -1.2   |
| IgA       | MEDI-551 300mg IV | 93     | -19                          | 17.6    | -78 | 15.3 | -18    |
|           | Placebo           | 25     | 5                            | 29.2    | -77 | 56.7 | 3.27   |
| IgE       | MEDI-551 300mg IV | 94     | -19                          | 93.5    | -95 | 553  | -36    |
|           | Placebo           | 25     | 108                          | 407     | -87 | 1700 | 1.96   |

Source: PARAM\_TOTALIG, IgG, IgM, IgA, IgE Subset of EPOCH\_RCP Subset of ADLBIG PCHG By (AVISIT, TRT01A).jmp

At the time of the 120-day safety update, the decrease in total immune globulins ([Table 61](#)) was continuing. The same is true for IgG, IgM ([Table 62](#)), IgA, and IgE.

**Table 61: Percent change from baseline, total immune globulins, by visit, all inebilizumab, mITT**

| Analysis Visit | Percent Change from Baseline |      |         |        |
|----------------|------------------------------|------|---------|--------|
|                | N                            | Mean | Std Dev | Median |
| Week 12        | 258                          | -3.3 | 19      | -6     |
| Week 28        | 171                          | -6.2 | 21.4    | -8.1   |
| Week 0 OLP     | 129                          | -11  | 22      | -10    |
| Week 13 OLP    | 231                          | -13  | 22.2    | -14    |
| Week 26 OLP    | 221                          | -12  | 21.9    | -13    |
| Week 39 OLP    | 174                          | -17  | 22.6    | -17    |
| Week 52 OLP    | 160                          | -20  | 20.1    | -19    |
| Week 65 OLP    | 133                          | -22  | 18.2    | -22    |
| Week 78 OLP    | 123                          | -24  | 17.3    | -24    |
| Week 91 OLP    | 112                          | -26  | 15.4    | -25    |
| Week 104 OLP   | 100                          | -26  | 16.8    | -24    |
| Week 117 OLP   | 87                           | -27  | 16.4    | -27    |
| Week 130 OLP   | 64                           | -30  | 15.6    | -31    |
| Week 143 OLP   | 43                           | -34  | 15.4    | -35    |
| Week 156 OLP   | 30                           | -36  | 11.3    | -38    |
| Week 169 OLP   | 18                           | -38  | 12.5    | -39    |
| Week 182 OLP   | 14                           | -39  | 10.9    | -39    |
| Week 195 OLP   | 1                            | -49  |         | -49    |
| Week 208 OLP   | 2                            | -54  | 2.79    | -54    |

Source: PARAM\_TOTAL Ig Subset of ADLBIG 120 day update PCHG By (AVISITN).jmp

**Table 62: Percent change from baseline in IgM levels, all inebilizumab group, by visit, mITT**

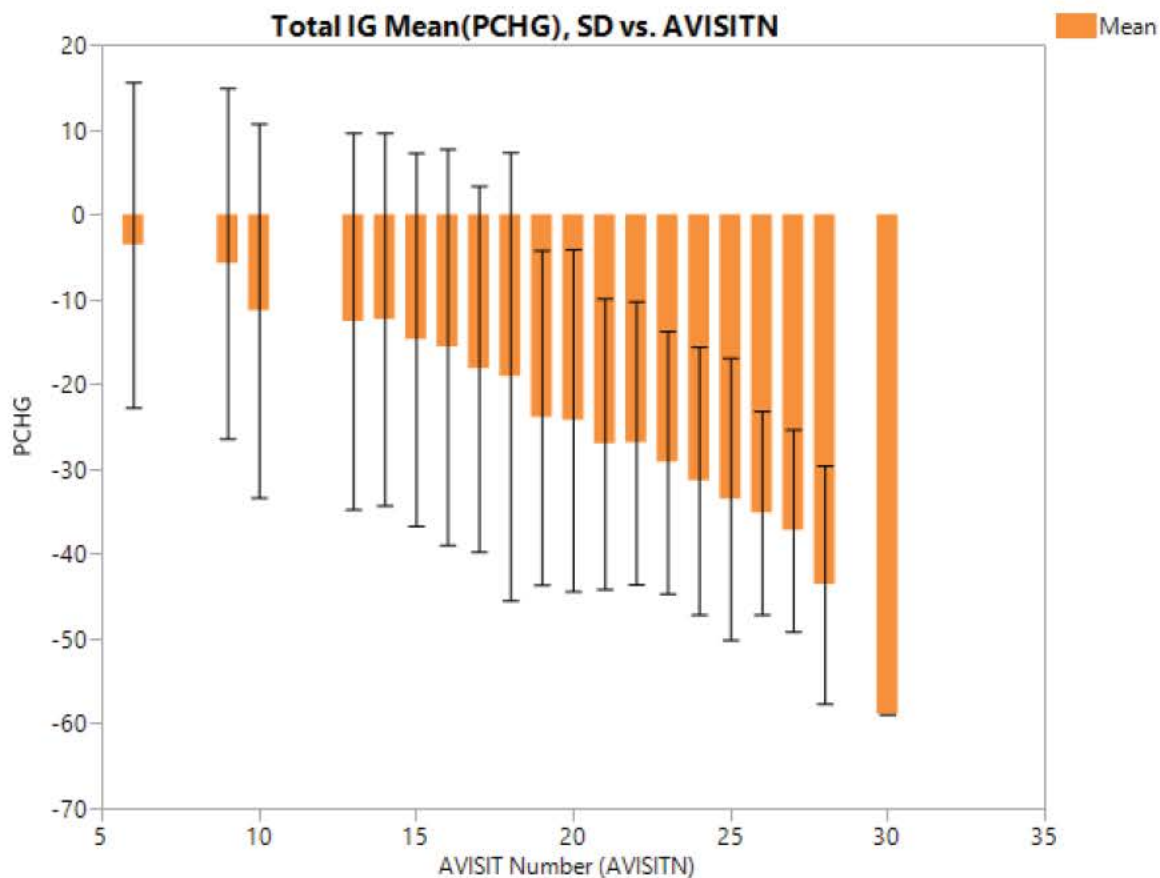
| Analysis visit | Percent change from baseline |      |         |        |
|----------------|------------------------------|------|---------|--------|
|                | N Rows                       | Mean | Std Dev | Median |
| Week 12        | 258                          | -15  | 30.2    | -18    |
| Week 28        | 171                          | -24  | 32.3    | -27    |
| Week 0 OLP     | 129                          | -23  | 30.2    | -23    |
| Week 13 OLP    | 232                          | -34  | 27.3    | -33    |
| Week 26 OLP    | 221                          | -37  | 25.7    | -38    |
| Week 39 OLP    | 174                          | -42  | 24.9    | -44    |
| Week 52 OLP    | 160                          | -45  | 20.6    | -46    |
| Week 65 OLP    | 133                          | -48  | 21.5    | -48    |
| Week 78 OLP    | 123                          | -49  | 21.6    | -52    |
| Week 91 OLP    | 112                          | -50  | 19.8    | -52    |
| Week 104 OLP   | 100                          | -50  | 20.4    | -51    |
| Week 117 OLP   | 87                           | -52  | 18.3    | -51    |
| Week 130 OLP   | 64                           | -55  | 17.6    | -56    |
| Week 143 OLP   | 43                           | -58  | 16.6    | -60    |
| Week 156 OLP   | 30                           | -58  | 17      | -63    |
| Week 169 OLP   | 18                           | -66  | 16.7    | -68    |
| Week 182 OLP   | 14                           | -62  | 17      | -68    |

Source: PARAM\_IgM Subset of ADLBIG 120 day update PCHG By (AVISITN).jmp

*Reviewer Comment: The gradual decrease in immune globulins with continuing treatment is a concern. Longer duration follow-up in a larger number of patients being treated with inebilizumab will be an important. The sponsor was asked to provide any additional information on immunoglobulin levels beyond that provided in the 120-day safety update. These data were provided in e0023 and are summarized in the graphs below. Levels of IgG, IgM, IgA and total IgG,M,A all appear to continue to decline over time although the number of observations in the latest time windows remains relatively small. Nevertheless, there is a serious concern for the potential for serious and opportunistic infections over time.*

Total immunoglobulins G, M and A

**Figure 15: Total IgG, IgM, IgA, by analysis visit, any inebilizumab population, post-120-day update**



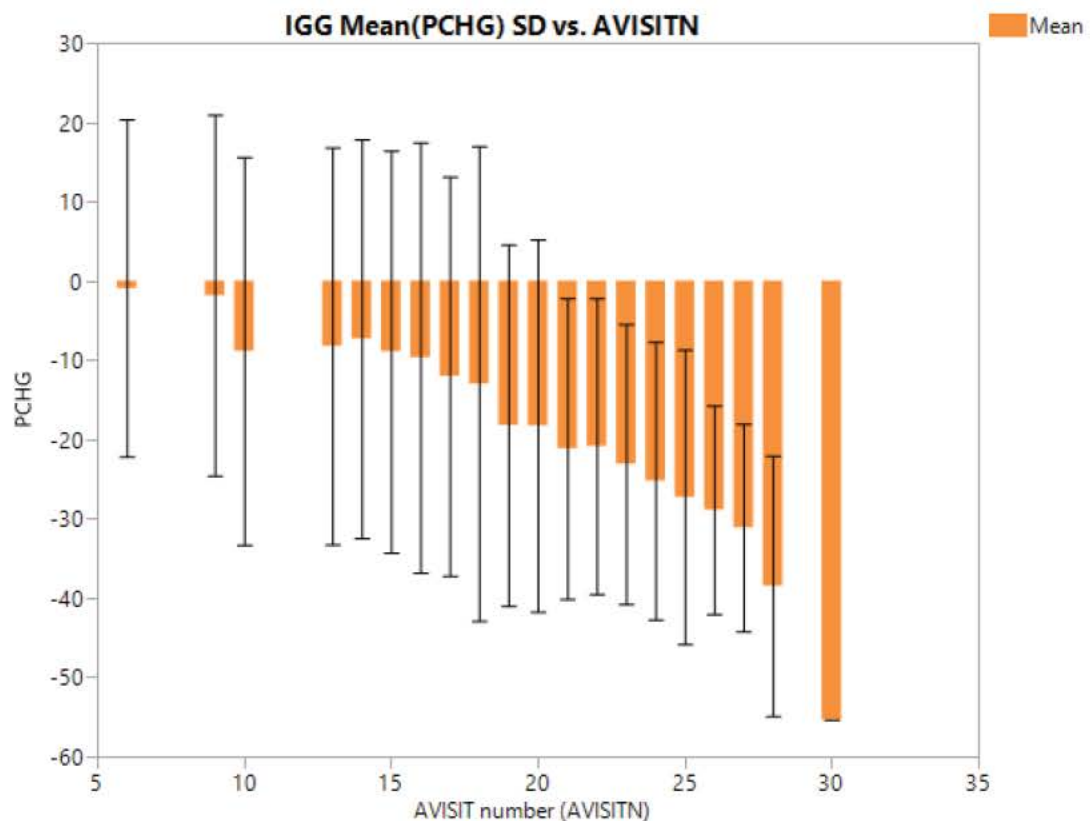
Source: LBTEST\_IgGlgMIgA total Subset of ANYMGFL\_Y Subset of ADLBIG updated e0023.jmp

| AVISITN | AVISIT         |
|---------|----------------|
| 1       | Week 0         |
| 6       | Week 12        |
| 9       | Week 28        |
| 13      | Week 13 (OLP)  |
| 14      | Week 26 (OLP)  |
| 15      | Week 39 (OLP)  |
| 16      | Week 52 (OLP)  |
| 17      | Week 65 (OLP)  |
| 18      | Week 78 (OLP)  |
| 19      | Week 91 (OLP)  |
| 20      | Week 104 (OLP) |

| AVISITN | AVISIT         |
|---------|----------------|
| 21      | Week 117 (OLP) |
| 22      | Week 130 (OLP) |
| 23      | Week 143 (OLP) |
| 24      | Week 156 (OLP) |
| 25      | Week 169 (OLP) |
| 26      | Week 182 (OLP) |
| 27      | Week 195 (OLP) |
| 28      | Week 208 (OLP) |
| 29      | Week 221 (OLP) |
| 30      | Week 234 (OLP) |

IgG

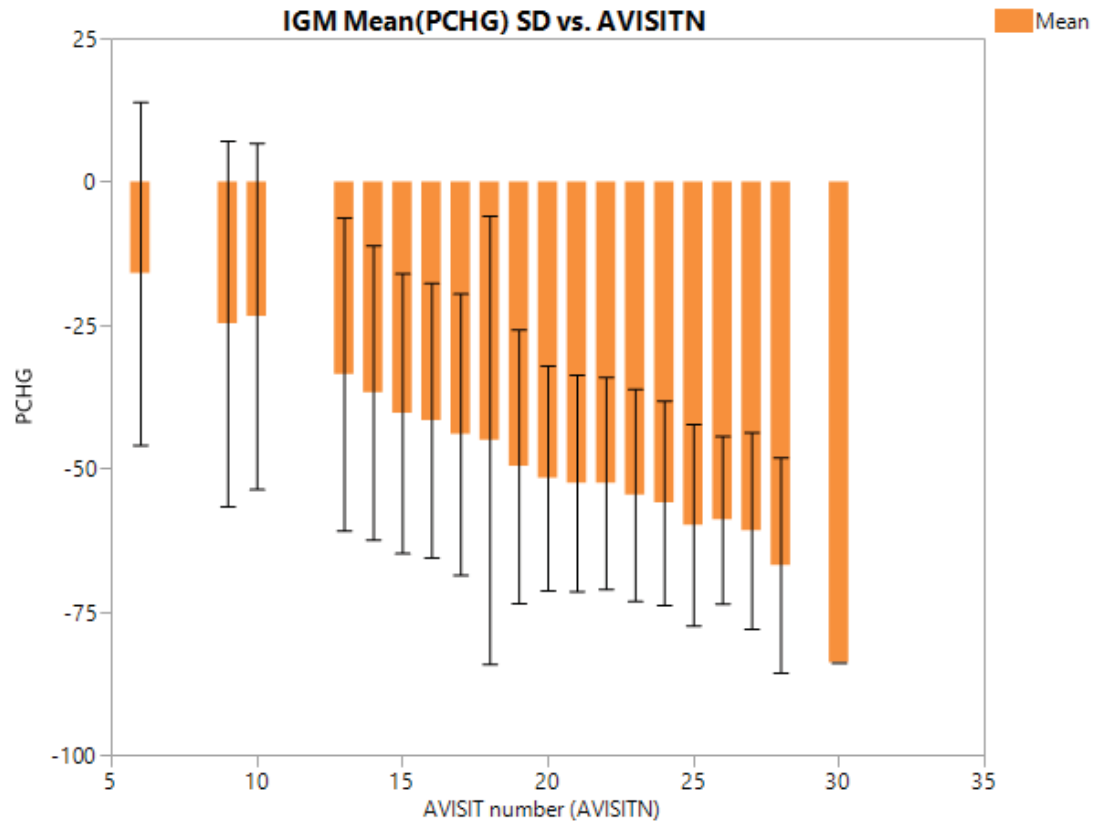
**Figure 16: IgG by analysis visit, any inebilizumab population, post-120-day safety update**



Source: LBTEST\_IGG Subset of ANYMGFL\_Y Subset of ADLBIG updated e0023.jmp

IgM

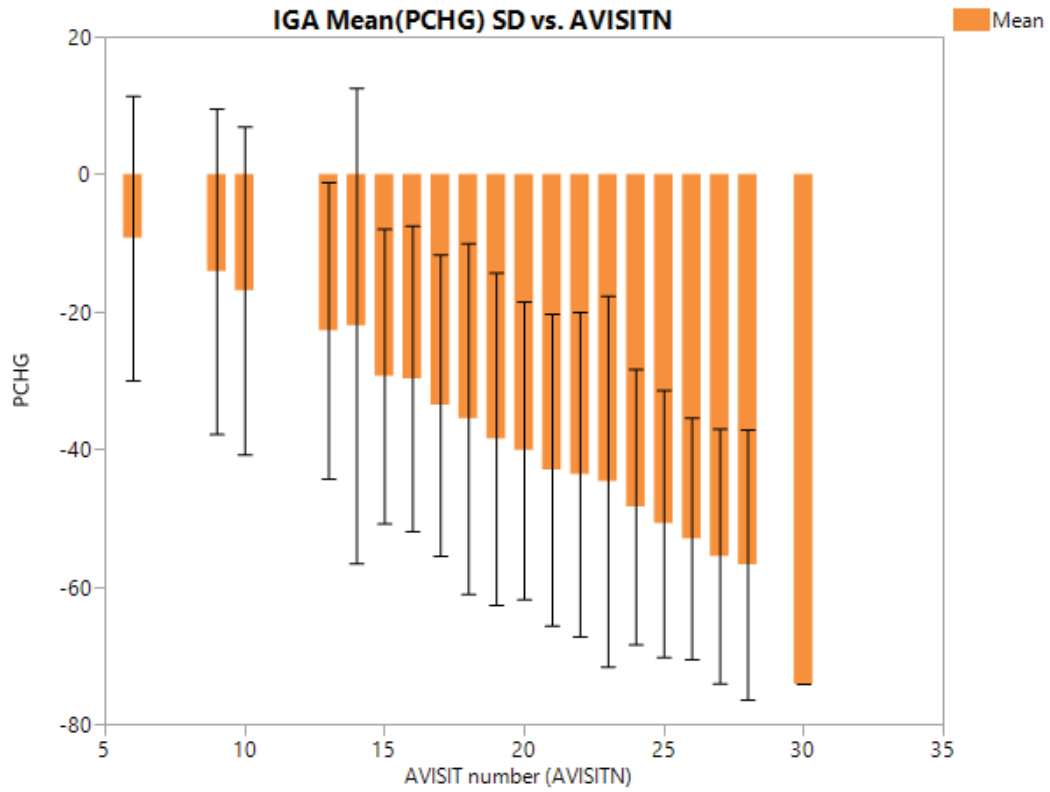
**Figure 17: IgM by analysis visit, any inebilizumab population, post-120 day safety update**



**Source:** LBTEST\_IGM Subset of ANYMGFL\_Y Subset of ADLBIG updated e0023.jmp

IgA

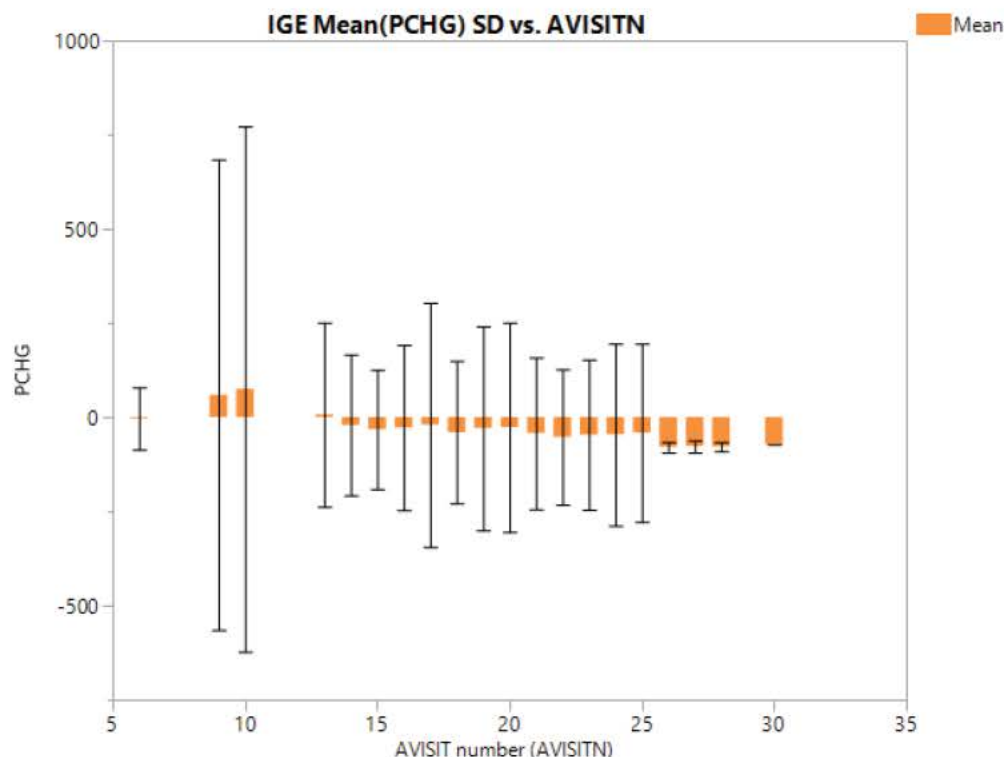
**Figure 18: IgA by analysis visit, any inebilizumab population, post-120-day safety update**



Source: LBTEST\_IGA Subset of ANYMGFL\_Y Subset of ADLBIG updated e0023.jmp

## IgE

**Figure 19: IgE by analysis visit, any inebilizumab population, post-120-day safety update**



Source: LBTEST\_IGE Subset of ANYMGFL\_Y Subset of ADLBIG updated e0023.jmp

### Anti-tetanus toxoid IgG

At week 28 of the RCP there was no significant change in the level of anti-tetanus toxoid IgG in those who were seropositive at baseline (Table 63). The same was true up to the time of the 120-day safety update.

**Table 63: Percent change from baseline in anti-tetanus toxoid IgG at week 28 of the RCP**

| TRT01A            | N Rows | Percent Change from Baseline |         |        |
|-------------------|--------|------------------------------|---------|--------|
|                   |        | Mean                         | Std Dev | Median |
| MEDI-551 300mg IV | 88     | 14.2                         | 36.8    | 7.37   |
| Placebo           | 24     | -8                           | 26.4    | -6.7   |

Source: PARAM\_ANTITET Subset of EPOCH\_RCP Subset of ADLBIG PCHG By (AVISIT, TRT01A).jmp

### 8.4.7. Vital Signs

### Blood pressure and pulse rate

During the RCP, there were no major differences in the incidence of blood pressure or pulse rate above or below the criteria for potentially significant changes ([Table 64](#)).

**Table 64: Blood pressure and Pulse rate**

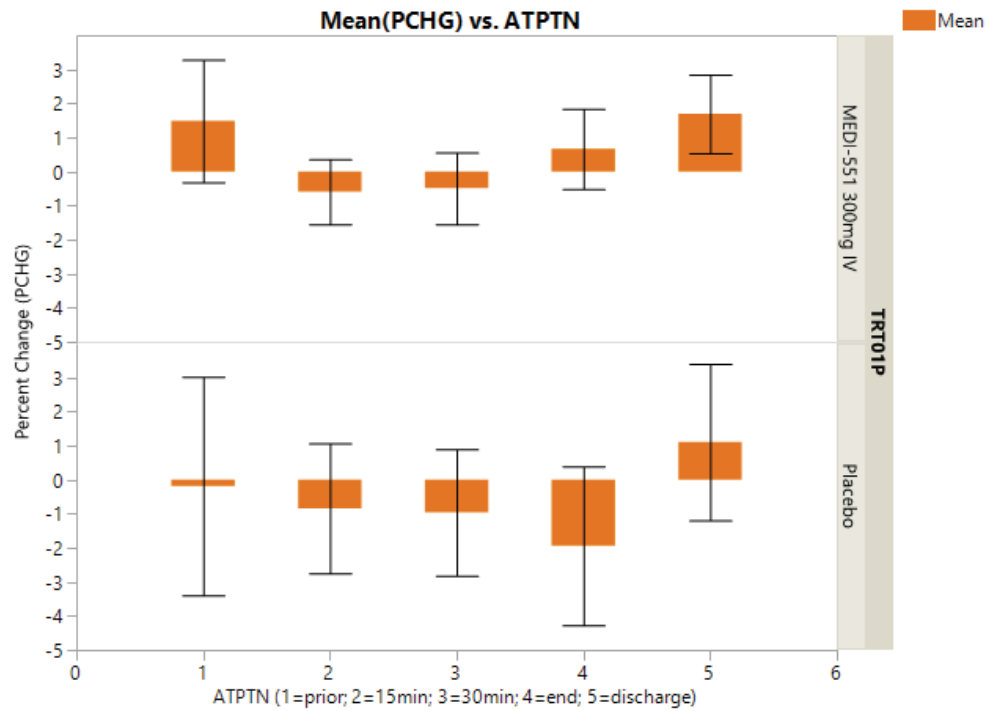
| Parameter             | Inebilizumab 300 mg IV | Placebo |
|-----------------------|------------------------|---------|
| SBP $\geq 140$        | 28.2                   | 41.1    |
| SBP $\geq 160$        | 5.8                    | 7.1     |
| SBP $\leq 90$         | 16.7                   | 23.2    |
| DBP $\leq 50$         | 10.4                   | 16.1    |
| DBP $\geq 90$         | 27.0                   | 50.0    |
| DBP $\geq 100$        | 7.5                    | 7.1     |
| Pulse rate $\leq 60$  | 42.0                   | 39.3    |
| Pulse rate $\geq 100$ | 12.6                   | 21.4    |

Source: AVAL of Subset of EPOCH\_RCP Subset of ADVS By (TRT01A, USUBJID) By (TRT01A).jmp

### Blood pressure changes during infusion

Systolic ([Figure 20](#)) and Diastolic ([Figure 21](#)) blood pressure changes during infusion of inebilizumab were relatively minor and not significantly different from the changes seen with the placebo infusion.

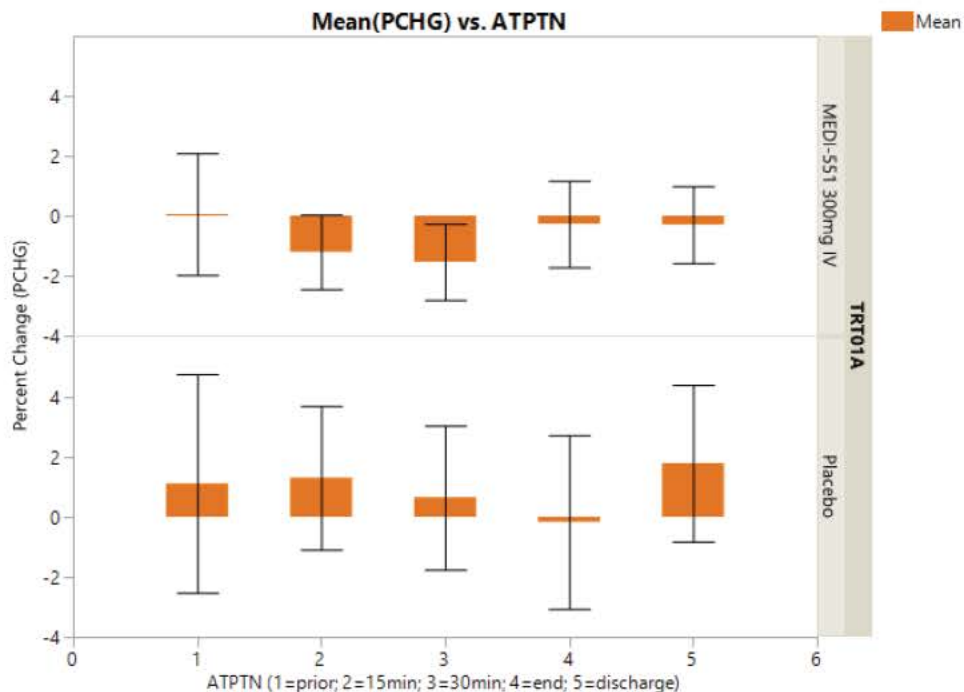
**Figure 20: Systolic Blood pressure, percent change during infusion**



Each error bar is constructed using a 95% confidence interval of the mean.

Source: ATPT\_Dosing Subset of SBP Subset of EPOCH\_RCP Subset of ADVS.jmp

**Figure 21: Diastolic blood pressure, percent change during infusion**



Each error bar is constructed using a 95% confidence interval of the mean.

**Source:** ATPTN Subset of DBP Subset of EPOCH\_RCP Subset of ADVS.jmp

#### 8.4.8. Electrocardiograms (ECGs)

#### 8.4.9. QT

There were no notable changes in the QT interval, Fridericia correction, during treatment with inebilizumab ([Table 65](#)).

**Table 65: QTcF during randomized treatment by actual treatment group**

| QTcF      | Inebilizumab | Placebo   |
|-----------|--------------|-----------|
| >450 msec | 12 (6.9%)    | 9 (16.1%) |
| >480 msec | 2 (1.2%)     | 8 (14.3%) |
| >500 msec | 1 (0.6%)     | 7 (12.5%) |

**Source:** PARAM\_QTc over 450, 480,500 Subsets of ADEG By (TRT01A, USUBJID) By (TRT01A).jmp

*Reviewer Comment: For those subject with a prolongation of >450msec., no single concomitant medication was prominent. Four of the 12 inebilizumab subjects and 4 of 9 placebo subjects were taking proton pump inhibitors.*

#### 8.4.10. Immunogenicity

The presence of anti-drug antibodies at any time during the RCP is shown in [Table 66](#). The assay used appears to be unreliable since ADA were detected in subject not being treated with inebilizumab.

**Table 66: ADA status, any time during RCP, mITT**

| ADASTCAT | N Rows |        | MEDI-551 300mg IV |        | Placebo |        |
|----------|--------|--------|-------------------|--------|---------|--------|
|          | N      | %      | N                 | %      | N       | %      |
| NEGATIVE | 205    | 89.1%  | 157               | 90.2%  | 48      | 85.7%  |
| POSITIVE | 25     | 10.9%  | 17                | 9.8%   | 8       | 14.3%  |
| Total    | 230    | 100.0% | 174               | 100.0% | 56      | 100.0% |

Source: ASTRFL\_Y Subset of ADSL TRT01A By (ADASTCAT) 2

### 8.5. Analysis of Submission-Specific Safety Issues

#### 8.5.1. Progressive Multifocal Leukoencephalopathy

There were four subjects who were evaluated for possible PML:

Subject (b) (6) – see [8.4.1](#)

*Reviewer Comment: The clinical events and MRI change for the above subject s are typical of PML. JC virus was not detected at the NIH laboratory. By the criteria of Berger et al.<sup>24</sup>, this event would be considered “possible PML.”*

Subject (b) (6)

This 32-year old female subject was enrolled earlier as (b) (6) but had an NMO attack of optic neuritis before randomization – an event that started on (b) (6) and ended on (b) (6). This subject was anti-AQP4-IgG negative at enrollment. The subject was subsequently randomized and treated with inebilizumab on (b) (6); the last dose was on (b) (6). There had been a non-serious AE of a seizure on (b) (6) (there was a history of a seizure prior to enrollment), a non-serious AE of eye inflammation on (b) (6) and a serious AE of blurred vision from (b) (6) to (b) (6). On (b) (6), the subject was hospitalized for further investigation. On

(b) (6) brain MRI showed hyperintensities which were more prominent than on the previous study performed on (b) (6), with the appearance of new hyperintense changes near the fourth ventricle and the periventricular area on the left side near the posterior aspect, the left frontal area near the ventricle, and a few new hyperintense changes in the posterior aspect near the ventricles on the right side. The previously reported hyperintensity along the left optic nerve appeared improved compared to prior test. On (b) (6) CSF examination was performed; results included glucose 45 mg/dl, protein 34.0 mg/dl, leukocytes 13, polymorphonuclear cells 30%, mononuclear cells 70%, and red blood cells 0. CSF oligoclonal bands of IgG class were not present. CSF JCV polymerase chain reaction was negative (b) (4). Blood anti-MOG (myelin oligodendrocyte glycoprotein) test was positive. A cell-based assay for anti-AQP4-IgG was negative. The latter two tests were performed at (b) (4). The subject was treated with intravenous immunoglobulin.

*Reviewer Comment: The clinical events do not suggest a specific diagnosis, but the MRI changes are not typical of PML and the CSF PCR for JCV DNA was negative. The presence of anti-MOG antibodies suggests that this was an acute demyelinating event and that this subject may not have had NMOSD despite an earlier positive test for anti-AQP4 IgG antibodies.*

Subject (b) (6)

This 48-year old female was randomized on (b) (6). Informed consent for the open label phase of the trial and received the first open-label dose of MEDI-551 on (b) (6) and the last dose of MEDI-551 prior to SAE onset on (b) (6). The subject discontinued the open-label period on (b) (6). On (b) (6), the subject experienced fever, which was grade 2 in severity. The subject reported that on (b) (6) she experienced breathing difficulties, coughing, fatigue, dizziness, instability when walking, unintentional weight loss and fever. On (b) (6), the subject developed respiratory failure which was grade 4 in severity and required hospitalization. On (b) (6), her condition worsened, and she was subsequently admitted to the intensive care unit for diagnosis and treatment. On the same date, a heart and lung X-ray showed pulmonary emphysema, peribronchial changes in perihilar and paracardiac regions and pleural adhesions base of left side of chest. On (b) (6), a sputum culture was positive for Streptococcus pneumoniae and on (b) (6), a sputum culture was positive for Haemophilus influenzae and Candida albicans. A serum test for JCV was performed and was positive (index value of 2.41). On (b) (6), a head a neck magnetic resonance imaging scan was performed which showed poorly defined, irregularly-shaped areas of changed signal intensity in the white matter in the left supratentorial, temporal and periventricular regions and the right anterior corpus callosum. The lesions had high signal intensity in T2 and FLAIR and were hypo-intense in T1-weighted images. The transverse size of the spinal cord was increased, and its structure pathologically changed. The central canal was dilated. An irregularly shaped, poorly defined area of changed signal intensity was visible in the medulla spinalis from the dens axis to the upper edge of C6.

Neurological status showed pyramidal tract syndrome, with brisk deep tendon reflexes in all four extremities, expanded reflexogenic zones, abdominal areflexia on all three levels, discrete intention tremor, finger-to-nose test bilaterally, adiadochokinesia bilaterally, dysesthesia in right half of body and urine retention. On (b) (6) lymphocyte percentage was 8.8% (reference range 20-40). On (b) (6), the subject was hospitalized to follow-up on the event of respiratory failure and to evaluate immune status. Laboratory tests for immune function were performed and were notable for normal levels of IgG, IgA, IgM, C3, C4. Total CD3+ T lymphocytes were 493 (normal range 1,050-1,980; units not specified). CD19+ B cells were 0 (normal range 110-350, units not specified). A course of treatment with 15 g human immunoglobulins by IV was administered. The subject was hospitalized on multiple subsequent occasions from (b) (6) (b) (6) for symptomatic treatment of immunosuppression. The AE of immunosuppression was considered recovered on (b) (6).

*Reviewer Comment: The new neurologic deficits and MRI lesions are compatible with NMOSD. In response to a request for follow-up information, the sponsor provided the CSF JCV which was negative on October 20, 2019. The site reported that, as of November 14, 2019, there were no clinical signs of PML.*

Subject (b) (6)

This 60-year old subject received the first dose of investigational product on (b) (6). The subject transitioned to the open-label period and began receiving open-label inebilizumab on (b) (6). The subject received the last dose of the investigational on (b) (6). The subject's medical history included deep vein thrombosis (1998), esophageal stenosis (1998), osteopenia (2014), hypertension (2010), myasthenia gravis (2004), antiphospholipid syndrome (1998), and systemic lupus (2014). Before entering the study, the subject had not received any chronic immunosuppression treatment for systemic lupus or myasthenia gravis. Prior to study entry, the subject was treated with prednisone for prevention of NMO relapses from (b) (6) until (b) (6) at which time she entered the study. On (b) (6) the subject had an assessment visit for a possible neuromyelitis optica spectrum disorder (NMOSD) attack and was admitted to the hospital. A study brain magnetic resonance imaging (MRI) done on that date showed extensive T2 hyperintense subcortical lesions in both occipital regions as well as one hyperintense T2 lesion in the left cerebellar hemisphere. Findings were assessed as an adverse event of special interest (AESI) of possible progressive multifocal leukoencephalopathy (PML). The subject did not present with a fever or other symptoms associated with possible PML. She did not have any changes in cognitive function. The patient remained hospitalized for treatment of NMOSD attack including methylprednisolone 1000 mg daily intravenously from (b) (6) (b) (6) and 250 mg daily from (b) (6), 60 mg daily to (b) (6), reduced to 40 mg daily, from (b) (6), ongoing. The patient also underwent seven courses of plasma exchange. On (b) (6), cerebrospinal fluid (CSF) analysis (including glucose, proteins and cell count) was normal. A JC virus PCR test on the cerebrospinal fluid was negative on (b) (6) (b) (4).

(b) (4)). The site confirmed on November 14, 2019 that the subject still has no symptoms that would be suggestive of PML.

*Reviewer Comment: Although the MRI changes would be compatible with PML, they could also be attributed to an NMOSD attack. The clinical symptoms and signs were minimal and the CSF JCV was negative.*

#### 8.5.2. Infections

There were no serious adverse events considered opportunistic infections during the RCP or in the any inebilizumab population. The most frequent nonserious events considered opportunistic were influenza and herpes infections. At the time of the 120-day safety update, there was one serious herpes zoster infection, 7 nonserious herpes infections (2 herpes zoster and 5 oral herpes) and 16 subjects with influenza.

*Reviewer Comment: There is no indication of a serious concern for opportunistic infections. However, the duration of observation is comparatively short and the population small.*

#### 8.5.3. Infusion-related reactions

In Study MI-CP200, a single dose phase 1 study in patients with scleroderma, the first subject at a dose of 3 mg/kg had a reaction during the infusion of moderate severity. Subsequently, the protocol was amended to include pretreatment to prevent such reactions. All subjects in the subsequent phase 1 study in MS patients were premedicated.

During the RCP, an AE of infusion related reaction was reported in 16 subjects (9.2%) treated with inebilizumab and in 6 subjects (10.7%) treated with placebo. None were considered serious in either group. The severity grade was 1 for all in the placebo group and for 15/16 in the inebilizumab group (one was grade 2). For the any inebilizumab group, the incidence of an infusion related reaction was 11.1% plus one event of “hypersensitivity”. At the time of the 120-day safety update 12% of subjects had an infusion-related reaction plus one case of “hypersensitivity”.

*Reviewer Comment: With pre-treatment, infusion related reactions with inebilizumab treatment do not appear to be a concern.*

#### 8.5.4. Immunosuppression

There is one case of symptomatic immune suppression with multiple episodes of pneumonia (see [13.8.3](#) for the full narrative).

Subject (b) (6) required treatment with intravenous immune globulins for an AE of immunosuppression. There had been multiple pulmonary infections requiring hospitalization and anti-microbial treatment. Immunoglobulin levels were normal as were CD3+ T-cell counts. During evaluation for the third episode of pneumonia, unintentional weight loss and fatigue, consultants determined that the recurrent infections were due to opportunistic organisms, e.g. Candida, due to immunosuppression. At last follow-up, his patient was being treated with monthly infusions of 15 grams of human immune globulins.

## 8.6. Safety Analyses by Demographic Subgroups

### By Sex

There were no obvious differences in the proportion of subjects with an AE by SOC. However, the relatively small proportion of subject who were male (approximately 10%) limits interpretation of any apparent differences, e.g. blood and lymphatic disorders, hepatobiliary disorders, vascular disorders.

**Table 67: Proportion of subjects with any AE, by SOC, any inebilizumab population**

| Body System or Organ Class                                          | F           | M          |
|---------------------------------------------------------------------|-------------|------------|
| Blood and lymphatic system disorders                                | 19 (9.1%)   | 0 (0.0%)   |
| Cardiac disorders                                                   | 7 (3.3%)    | 0 (0.0%)   |
| Congenital, familial and genetic disorders                          | 1 (0.5%)    | 0 (0.0%)   |
| Ear and labyrinth disorders                                         | 13 (6.2%)   | 2 (9.5%)   |
| Endocrine disorders                                                 | 5 (2.4%)    | 0 (0.0%)   |
| Eye disorders                                                       | 29 (13.9%)  | 1 (4.8%)   |
| Gastrointestinal disorders                                          | 62 (29.7%)  | 7 (33.3%)  |
| General disorders and administration site conditions                | 47 (22.5%)  | 3 (14.3%)  |
| Hepatobiliary disorders                                             | 9 (4.3%)    | 0 (0.0%)   |
| Immune system disorders                                             | 5 (2.4%)    | 0 (0.0%)   |
| Infections and infestations                                         | 136 (65.1%) | 12 (57.1%) |
| Injury, poisoning and procedural complications                      | 56 (26.8%)  | 4 (19.0%)  |
| Investigations                                                      | 30 (14.4%)  | 3 (14.3%)  |
| Metabolism and nutrition disorders                                  | 21 (10.0%)  | 2 (9.5%)   |
| Musculoskeletal and connective tissue disorders                     | 70 (33.5%)  | 11 (52.4%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 5 (2.4%)    | 0 (0.0%)   |
| Nervous system disorders                                            | 68 (32.5%)  | 8 (38.1%)  |
| Product issues                                                      | 0 (0.0%)    | 1 (4.8%)   |
| Psychiatric disorders                                               | 33 (15.8%)  | 3 (14.3%)  |
| Renal and urinary disorders                                         | 20 (9.6%)   | 2 (9.5%)   |
| Reproductive system and breast disorders                            | 8 (3.8%)    | 3 (14.3%)  |
| Respiratory, thoracic and mediastinal disorders                     | 34 (16.3%)  | 3 (14.3%)  |
| Skin and subcutaneous tissue disorders                              | 53 (25.4%)  | 3 (14.3%)  |
| Vascular disorders                                                  | 13 (6.2%)   | 0 (0.0%)   |
| Subjects(filtered)                                                  | 182 (87.1%) | 20 (95.2%) |

| Body System or Organ Class | F            | M           |
|----------------------------|--------------|-------------|
| 1stCollItemSubjects        | 209 (100.0%) | 21 (100.0%) |

Source: JRevSelASTRFL\_Y SexbySOCfiltANL04FL\_Y

*Reviewer Comment: There are too few subjects in the older age categories (only 10 subjects age 65 or over).*

**Table 68: Adverse events by SOC, by ethnic group, any inebilizumab population**

| Body System or Organ Class                                          | HISPANIC OR LATINO | NOT HISPANIC OR LATINO |
|---------------------------------------------------------------------|--------------------|------------------------|
| Blood and lymphatic system disorders                                | 5 (11.6%)          | 14 (7.5%)              |
| Cardiac disorders                                                   | 0 (0.0%)           | 7 (3.7%)               |
| Congenital, familial and genetic disorders                          | 0 (0.0%)           | 1 (0.5%)               |
| Ear and labyrinth disorders                                         | 1 (2.3%)           | 14 (7.5%)              |
| Endocrine disorders                                                 | 0 (0.0%)           | 5 (2.7%)               |
| Eye disorders                                                       | 10 (23.3%)         | 20 (10.7%)             |
| Gastrointestinal disorders                                          | 13 (30.2%)         | 56 (29.9%)             |
| General disorders and administration site conditions                | 6 (14.0%)          | 44 (23.5%)             |
| Hepatobiliary disorders                                             | 1 (2.3%)           | 8 (4.3%)               |
| Immune system disorders                                             | 0 (0.0%)           | 5 (2.7%)               |
| Infections and infestations                                         | 31 (72.1%)         | 117 (62.6%)            |
| Injury, poisoning and procedural complications                      | 13 (30.2%)         | 47 (25.1%)             |
| Investigations                                                      | 5 (11.6%)          | 28 (15.0%)             |
| Metabolism and nutrition disorders                                  | 0 (0.0%)           | 23 (12.3%)             |
| Musculoskeletal and connective tissue disorders                     | 10 (23.3%)         | 71 (38.0%)             |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 (0.0%)           | 5 (2.7%)               |
| Nervous system disorders                                            | 17 (39.5%)         | 59 (31.6%)             |
| Product issues                                                      | 0 (0.0%)           | 1 (0.5%)               |
| Psychiatric disorders                                               | 2 (4.7%)           | 34 (18.2%)             |
| Renal and urinary disorders                                         | 4 (9.3%)           | 18 (9.6%)              |
| Reproductive system and breast disorders                            | 4 (9.3%)           | 7 (3.7%)               |
| Respiratory, thoracic and mediastinal disorders                     | 4 (9.3%)           | 33 (17.6%)             |
| Skin and subcutaneous tissue disorders                              | 5 (11.6%)          | 51 (27.3%)             |
| Vascular disorders                                                  | 4 (9.3%)           | 9 (4.8%)               |
| Subjects(filtered)                                                  | 38 (88.4%)         | 164 (87.7%)            |
| 1stCollItemSubjects                                                 | 43 (100.0%)        | 187 (100.0%)           |

Source: JRevSelASTRFL\_Y ETHNICITYbySOCfiltANL04FL\_Y

## By Region

The overall incidence of any AE did not vary significantly by region. There was some variability within individual SOC's but this was not consistent and most likely attributable to relatively few observations.

**Table 69: Adverse events, by Region3, any inebilizumab population**

| Body System or Organ Class                                          | Europe and Israel | North America | Pan-Pacific and Asia | Rest of the World |
|---------------------------------------------------------------------|-------------------|---------------|----------------------|-------------------|
| Blood and lymphatic system disorders                                | 9 (9.6%)          | 1 (2.3%)      | 3 (5.9%)             | 6 (14.3%)         |
| Cardiac disorders                                                   | 3 (3.2%)          | 3 (7.0%)      | 1 (2.0%)             | 0 (0.0%)          |
| Congenital, familial and genetic disorders                          | 0 (0.0%)          | 1 (2.3%)      | 0 (0.0%)             | 0 (0.0%)          |
| Ear and labyrinth disorders                                         | 6 (6.4%)          | 5 (11.6%)     | 3 (5.9%)             | 1 (2.4%)          |
| Endocrine disorders                                                 | 3 (3.2%)          | 0 (0.0%)      | 2 (3.9%)             | 0 (0.0%)          |
| Eye disorders                                                       | 6 (6.4%)          | 8 (18.6%)     | 7 (13.7%)            | 9 (21.4%)         |
| Gastrointestinal disorders                                          | 19 (20.2%)        | 17 (39.5%)    | 19 (37.3%)           | 14 (33.3%)        |
| General disorders and administration site conditions                | 14 (14.9%)        | 18 (41.9%)    | 13 (25.5%)           | 5 (11.9%)         |
| Hepatobiliary disorders                                             | 2 (2.1%)          | 1 (2.3%)      | 5 (9.8%)             | 1 (2.4%)          |
| Immune system disorders                                             | 2 (2.1%)          | 1 (2.3%)      | 2 (3.9%)             | 0 (0.0%)          |
| Infections and infestations                                         | 59 (62.8%)        | 34 (79.1%)    | 26 (51.0%)           | 29 (69.0%)        |
| Injury, poisoning and procedural complications                      | 15 (16.0%)        | 18 (41.9%)    | 13 (25.5%)           | 14 (33.3%)        |
| Investigations                                                      | 16 (17.0%)        | 12 (7.9%)     | 1 (2.0%)             | 4 (9.5%)          |
| Metabolism and nutrition disorders                                  | 9 (9.6%)          | 7 (16.3%)     | 6 (11.8%)            | 1 (2.4%)          |
| Musculoskeletal and connective tissue disorders                     | 24 (25.5%)        | 21 (48.8%)    | 26 (51.0%)           | 10 (23.8%)        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 (3.2%)          | 2 (4.7%)      | 0 (0.0%)             | 0 (0.0%)          |
| Nervous system disorders                                            | 28 (29.8%)        | 20 (46.5%)    | 12 (23.5%)           | 16 (38.1%)        |
| Product issues                                                      | 0 (0.0%)          | 0 (0.0%)      | 1 (2.0%)             | 0 (0.0%)          |
| Psychiatric disorders                                               | 12 (12.8%)        | 12 (27.9%)    | 10 (19.6%)           | 2 (4.8%)          |

| Body System or Organ Class                      | Europe and Israel | North America | Pan-Pacific and Asia | Rest of the World |
|-------------------------------------------------|-------------------|---------------|----------------------|-------------------|
| Renal and urinary disorders                     | 8 (8.5%)          | 10 (23.3%)    | 2 (3.9%)             | 2 (4.8%)          |
| Reproductive system and breast disorders        | 2 (2.1%)          | 3 (7.0%)      | 3 (5.9%)             | 3 (7.1%)          |
| Respiratory, thoracic and mediastinal disorders | 14 (14.9%)        | 9 (20.9%)     | 10 (19.6%)           | 4 (9.5%)          |
| Skin and subcutaneous tissue disorders          | 17 (18.1%)        | 19 (44.2%)    | 15 (29.4%)           | 5 (11.9%)         |
| Vascular disorders                              | 4 (4.3%)          | 5 (11.6%)     | 1 (2.0%)             | 3 (7.1%)          |
| Subjects(filtered) with an event                | 78 (83.0%)        | 41 (95.3%)    | 47 (92.2%)           | 36 (85.7%)        |
| 1stCollItemSubjects in category                 | 94 (100.0%)       | 43 (100.0%)   | 51 (100.0%)          | 42 (100.0%)       |

Source: JRevSelASTRFL\_Y REGION3bySOCfiltANL04FL\_Y

*Reviewer Comment: Similarly, there were no notable differences in the overall occurrence of AEs comparing US to OUS or Japan to non-Japan regions. There were too few SAEs to make valid comparisons by region.*

| Body System or Organ Class                           | AMERICAN INDIAN OR ALASKAN NATIVE | ASIAN      | BLACK OR AFRICAN AMERICAN | MULTIPLE CATEGORIES CHECKED | OTHER      | WHITE      |
|------------------------------------------------------|-----------------------------------|------------|---------------------------|-----------------------------|------------|------------|
| Blood and lymphatic system disorders                 | 2 (10.5%)                         | 3 (6.4%)   | 1 (5.0%)                  | 0 (0.0%)                    | 4 (17.4%)  | 9 (7.5%)   |
| Cardiac disorders                                    | 0 (0.0%)                          | 1 (2.1%)   | 1 (5.0%)                  | 0 (0.0%)                    | 0 (0.0%)   | 5 (4.2%)   |
| Congenital, familial and genetic disorders           | 0 (0.0%)                          | 0 (0.0%)   | 0 (0.0%)                  | 0 (0.0%)                    | 0 (0.0%)   | 1 (0.8%)   |
| Ear and labyrinth disorders                          | 0 (0.0%)                          | 2 (4.3%)   | 3 (15.0%)                 | 0 (0.0%)                    | 1 (4.3%)   | 9 (7.5%)   |
| Endocrine disorders                                  | 0 (0.0%)                          | 2 (4.3%)   | 0 (0.0%)                  | 0 (0.0%)                    | 0 (0.0%)   | 3 (2.5%)   |
| Eye disorders                                        | 0 (0.0%)                          | 7 (14.9%)  | 3 (15.0%)                 | 0 (0.0%)                    | 10 (43.5%) | 10 (8.3%)  |
| Gastrointestinal disorders                           | 3 (15.8%)                         | 18 (38.3%) | 10 (50.0%)                | 0 (0.0%)                    | 10 (43.5%) | 28 (23.3%) |
| General disorders and administration site conditions | 0 (0.0%)                          | 12 (25.5%) | 7 (35.0%)                 | 0 (0.0%)                    | 6 (26.1%)  | 25 (20.8%) |
| Hepatobiliary disorders                              | 1 (5.3%)                          | 5 (10.6%)  | 1 (5.0%)                  | 0 (0.0%)                    | 0 (0.0%)   | 2 (1.7%)   |
| Immune system disorders                              | 0 (0.0%)                          | 2 (4.3%)   | 0 (0.0%)                  | 0 (0.0%)                    | 0 (0.0%)   | 3 (2.5%)   |
| Infections and infestations                          | 13 (68.4%)                        | 24 (51.1%) | 14 (70.0%)                | 1 (100.0%)                  | 15 (65.2%) | 81 (67.5%) |
| Injury, poisoning and procedural complications       | 7 (36.8%)                         | 13 (27.7%) | 9 (45.0%)                 | 0 (0.0%)                    | 8 (34.8%)  | 23 (19.2%) |
| Investigations                                       | 1 (5.3%)                          | 1 (2.1%)   | 10 (50.0%)                | 0 (0.0%)                    | 3 (13.0%)  | 18 (15.0%) |
| Metabolism and nutrition disorders                   | 0 (0.0%)                          | 6 (12.8%)  | 3 (15.0%)                 | 0 (0.0%)                    | 1 (4.3%)   | 13 (10.8%) |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

| Body System or Organ Class                                          | AMERICAN<br>INDIAN OR<br>ALASKAN<br>NATIVE | ASIAN       | BLACK OR<br>AFRICAN<br>AMERICAN | MULTIPLE<br>CATEGORIES<br>CHECKED | OTHER       | WHITE        |
|---------------------------------------------------------------------|--------------------------------------------|-------------|---------------------------------|-----------------------------------|-------------|--------------|
| Musculoskeletal and connective tissue disorders                     | 0 (0.0%)                                   | 22 (46.8%)  | 8 (40.0%)                       | 0 (0.0%)                          | 10 (43.5%)  | 41 (34.2%)   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 (0.0%)                                   | 0 (0.0%)    | 2 (10.0%)                       | 0 (0.0%)                          | 0 (0.0%)    | 3 (2.5%)     |
| Nervous system disorders                                            | 4 (21.1%)                                  | 8 (17.0%)   | 8 (40.0%)                       | 0 (0.0%)                          | 13 (56.5%)  | 43 (35.8%)   |
| Product issues                                                      | 0 (0.0%)                                   | 1 (2.1%)    | 0 (0.0%)                        | 0 (0.0%)                          | 0 (0.0%)    | 0 (0.0%)     |
| Psychiatric disorders                                               | 0 (0.0%)                                   | 10 (21.3%)  | 4 (20.0%)                       | 0 (0.0%)                          | 2 (8.7%)    | 20 (16.7%)   |
| Renal and urinary disorders                                         | 0 (0.0%)                                   | 2 (4.3%)    | 3 (15.0%)                       | 0 (0.0%)                          | 2 (8.7%)    | 15 (12.5%)   |
| Reproductive system and breast disorders                            | 0 (0.0%)                                   | 3 (6.4%)    | 0 (0.0%)                        | 0 (0.0%)                          | 2 (8.7%)    | 6 (5.0%)     |
| Respiratory, thoracic and mediastinal disorders                     | 0 (0.0%)                                   | 9 (19.1%)   | 5 (25.0%)                       | 0 (0.0%)                          | 5 (21.7%)   | 18 (15.0%)   |
| Skin and subcutaneous tissue disorders                              | 0 (0.0%)                                   | 15 (31.9%)  | 9 (45.0%)                       | 0 (0.0%)                          | 5 (21.7%)   | 27 (22.5%)   |
| Vascular disorders                                                  | 1 (5.3%)                                   | 1 (2.1%)    | 2 (10.0%)                       | 0 (0.0%)                          | 2 (8.7%)    | 7 (5.8%)     |
| Subjects(filtered)                                                  | 17 (89.5%)                                 | 43 (91.5%)  | 18 (90.0%)                      | 1 (100.0%)                        | 19 (82.6%)  | 104 (86.7%)  |
| 1stCollItemSubjects                                                 | 19 (100.0%)                                | 47 (100.0%) | 20 (100.0%)                     | 1 (100.0%)                        | 23 (100.0%) | 120 (100.0%) |

Source: JRevSelASTRFL\_Y RACEbySOCfiltANL04FL\_Y

## 8.7. Specific Safety Studies/Clinical Trials

### 8.7.1. Study MI-CP200

Study MI-CP200 was a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability of escalating single IV doses of INEBILIZUMAB in adult subjects with Systemic Sclerosis (Scleroderma; SSc) who had at least moderate skin thickening in an area suitable for repeat biopsy. This was a single ascending dose study intended to assess the safety of inebilizumab. Five cohorts of subjects received one of 5 single IV doses of inebilizumab (0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo. Inebilizumab was administered as an IV infusion over a minimum of 60 minutes for all doses  $\leq 1.0$  mg/kg or over 120 minutes for all doses  $> 1.0$  mg/kg. Subjects were to be in the study for approximately 105 days (up to 21 days for screening and 84 days after administration of investigational product for follow-up). Subjects who required monitoring for B-cell recovery were continued for long-term follow-up (LTFU), which could have extended for more than 1 year.

*Reviewer Comment: The first subject in the 3.0 mg/kg cohort experienced an infusion related reaction of moderate intensity during administration of the investigational product. The protocol was amended (Protocol Amendment 3 and all subsequent subjects were premedicated with oral acetaminophen (500-650 mg) or equivalent dose of paracetamol, oral diphenhydramine (25-50 mg), and IV methylprednisolone or equivalent glucocorticoid (100 mg) 30 to 60 minutes prior to inebilizumab administration to minimize infusion related reactions.*

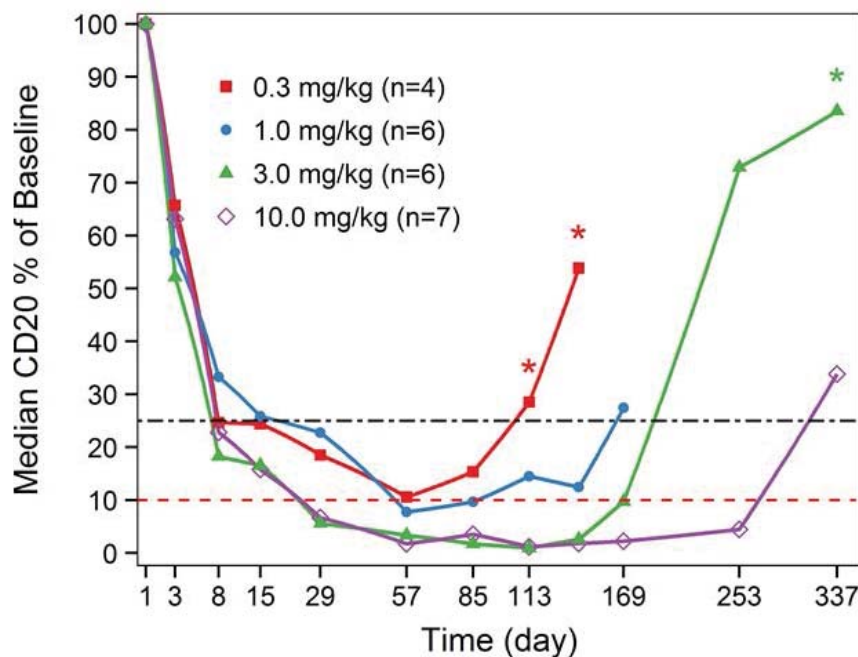
All subjects completed the study through Day 85, and 24 of 28 subjects (85.7%) completed the overall study. Long-term follow-up of subjects for B-cell recovery to baseline (Day 1) values occurred in 2 of 4 subjects in the placebo group and 22 of 24 subjects in the INEBILIZUMAB group (the 1 subject in the 0.1 mg/kg group; 3 of 4 subjects in the 0.3 mg/kg group; all 6 subjects in the 1.0 mg/kg group; 5 of 6 subjects in the 3.0 mg/kg group [1 subject died prior to LTFU]; and all 7 subjects in the 10.0 mg/kg group).

The extent of B-cell depletion as measured by maximum reduction from baseline was dose dependent, and the median reduction from baseline was 89.8%, 98.2%, 99.1%, and 99.7% for the 0.3, 1.0, 3.0, and 10.0 mg/kg IV doses, respectively. Except for the one subject in the 0.1 mg/kg dose cohort, whose B-cell count remained depleted about 30% of baseline after 3 years from treatment, all other subjects showed B-cell recovery. Full B-cell recovery for subjects in the lower dose cohorts occurred sometime after Day 169; whereas, full B-cell recovery for

subjects enrolled in the highest dose group was observed even later, around Day 337 and beyond ([Figure 22](#)).

*Reviewer Comment: The sponsor notes that depletion of B-cells was more pronounced in the higher dose groups and that the 3.0 and 10.0 mg/kg groups reached 90% depletion more rapidly than the lower dose groups.*

**Figure 22: Sponsor Figure 11.4.1.1-1 Median Depletion and Dose-dependent Recovery of CD20 B Cells in Subjects After Single IV Dose of INEBILIZUMAB Through Day 337 (0.3 to 10.0 mg/kg; As-treated Population)**



Anti-drug antibody to INEBILIZUMAB was detected in no subjects in the placebo group and 4/24 subjects (16.7%) in the total inebilizumab group. Among subjects who received a single dose of inebilizumab, all pre-dose ADA measurements were negative. Positive ADAs (defined as a titer of 50 or higher) were detected in 1 of 4 subjects (25.0%) in the 0.3 mg/kg dose group, 1 of 6 subjects (16.7%) in the 1.0 mg/kg dose group, 1 of 6 subjects (16.7%) in the 3.0 mg/kg dose group, and 1 of 7 subjects (14.3%) in the 10.0 mg/kg dose group.

All 4 ADA-positive subjects had reduced serum inebilizumab concentrations and faster clearance compared to ADA-negative subjects in the same dose group.

However, the presence of ADA had no impact on CD20 B-cell depletion or repletion. B-cell depletion was also observed in ADA-positive subjects. The B lymphocytes were depleted to a similar extent as in ADA-negative subjects.

#### Safety

*Reviewer Comment: Adverse events were collected for all subjects to day 85 and beyond day 85 for those being followed further for B-cell depletion. It should be noted that subjects who received higher doses often required prolonged follow-up due to persistent B-cell depletion.*

One subject in the 3.0 mg/kg INEBILIZUMAB group died due to scleroderma renal crisis, with onset on Day 62 that led to death 47 days later. The subject also had Grade 3 gastric antral vascular ectasia with onset on Day 62 and Grade 4 respiratory failure with onset on Day 67; neither the death nor TSEAs were assessed as related to investigational product by the investigator.

Treatment-emergent SAEs occurred in 6/24 subjects (25.0%), with 4/24 (16.7%) occurring between Days 1 and 85 and 2/24 (8.3%) occurring after Day 85. Subject (b) (6) in the 0.3 mg/kg INEBILIZUMAB group and Subject (b) (6) in the 1.0 mg/kg inebilizumab group had TSEAs (supraventricular tachycardia and subclavian vein thrombosis, respectively) that were considered related to investigational product by the investigator, although alternate etiologies were given for both events.

There were no TEAEs in the placebo group that occurred in more than one subject; in the total INEBILIZUMAB group, the most frequent (incidence > 15%) TEAEs by preferred term were arthralgia, fatigue, pain in extremity, infusion related reaction, and nausea, of which nausea and infusion related reaction only occurred in the total INEBILIZUMAB group

After Day 85, no additional TEAEs occurred in the placebo group and 23 additional TEAEs occurred in 8/24 subjects in the total INEBILIZUMAB group subjects in the higher-dose cohorts remained in the study longer than subjects in the lower-dose cohorts due to the longer duration of B-cell depletion in the higher-dose cohorts.

0.1 mg/kg inebilizumab : ischemic colitis, acute renal failure, atrial fibrillation, and prostate cancer (1 subject)

0.3 mg/kg inebilizumab : depression (1 subject)

1.0 mg/kg inebilizumab : cervical myelopathy, dysphagia, procedural pain (2 events), constipation (1 subject), and thermal burn (right thumb and pointer finger, 1 subject)

3.0 mg/kg inebilizumab: upper respiratory tract infection (3 events), cellulitis, arthralgia (1 subject), and diarrhea (2 events, 1 subject).

10.0 mg/kg inebilizumab: depression (1 subject), and colitis, skin ulcer, and non-cardiac chest pain (1 subject)

Infusion related reactions occurred in no subjects in the placebo group and 4/24 subjects (16.7%) in the total MEDI-551 group

There was no difference in the occurrence of serious infections by treatment group. Events of note were a prolonged upper respiratory infection, 3 cases of reactivation of herpes simplex. There were no cases of PML.

There were no significant findings from the results of the routine safety laboratory studies of from analysis of ECGs.

Of the 23 subjects who had at least one TEAE in the total inebilizumab group, TEAEs occurred in 4/23 subjects (17.4%) who were ADA positive and in 19/23 subjects (82.6%) who were ADA negative.

*Reviewer Comment: the sponsor similar trends toward a reduction in other types of adverse events in subjects who were positive for ADAs.*

#### 8.7.2. Study CD-IA-MEDI-551-1102

Study CD-IA-MEDI-551-1102 was a Phase 1, multicenter, multinational, randomized, blinded, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of IV or SC doses of MEDI-551 in adult subjects with relapsing forms of MS. RMS patients with at least one relapse in the previous 3 years and an EDSS score of less than 6.5 were eligible. There were to be 5 cohorts, 3 to receive fixed doses of the drug IV and 2 to receive fixed doses of the drug SC. The planned cohorts were:

- Cohort 1: 30 mg × 2 IV MEDI-551 (n = 6) or IV placebo × 2 (n = 2)
- Cohort 2: 100 mg × 2 IV MEDI-551 (n = 3) or IV placebo × 2 (n = 1)
- Cohort 3: 60 mg × 1 SC MEDI-551 (n = 3) or SC placebo × 1 (n = 1)
- Cohort 4: 300 mg × 1 SC MEDI-551 (n = 3) or SC placebo × 1 (n = 1)
- Cohort 5: 600 mg × 2 IV MEDI-551 (n = 6) or IV placebo × 2 (n = 2)

IV drug was administered on days 1 and 15. The infusion time to deliver the dose for Cohort 1 was anticipated to be approximately 150 minutes ± 15 minutes and 90 minutes ± 15 minutes for

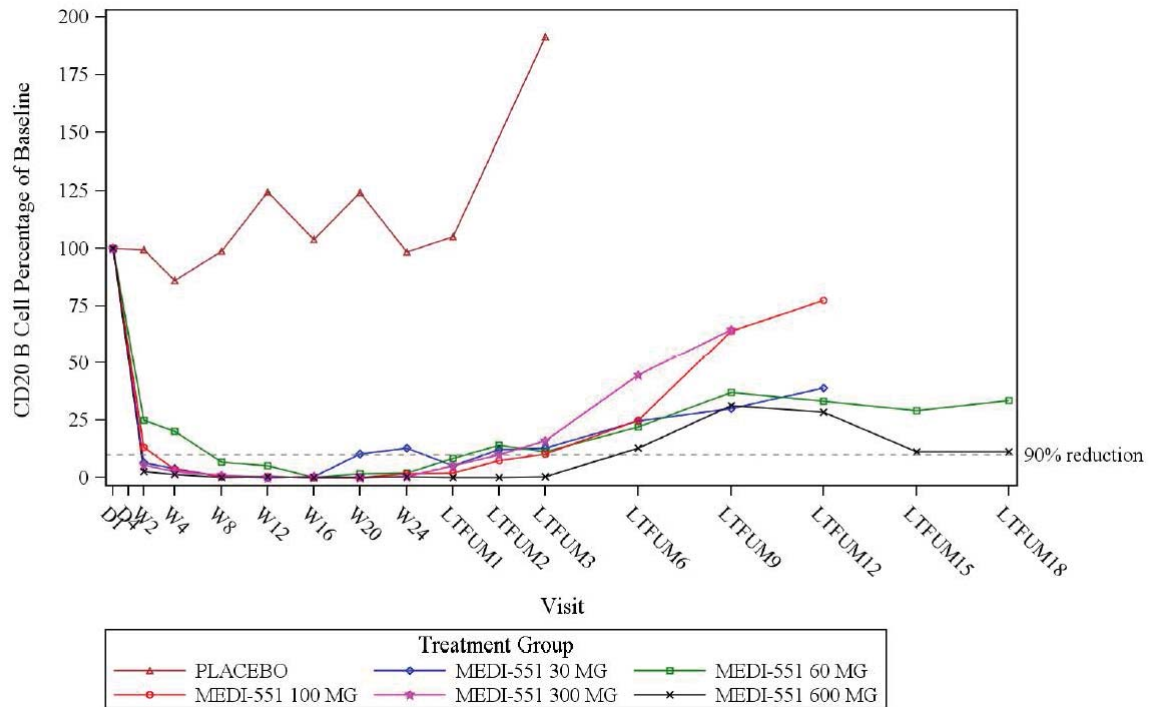
Cohorts 2 and 5. All subjects in the IV cohorts were premedicated with IV methylprednisolone (100 mg) or equivalent glucocorticoid, oral acetaminophen (500 - 650 mg) or equivalent dose of paracetamol, and oral diphenhydramine (25 - 50 mg) or equivalent antihistamine, 30 to 60 minutes prior to investigational product administration on Days 1 and 15 (Cohorts 1, 2, and 5) to minimize the occurrence of infusion reactions.

Twenty-seven of 28 subjects (96.4%) completed the protocol-defined end of treatment period (Day 169). One subject did not complete the treatment period due to death. Subject (b) (6) (MEDI-551 30 mg IV group) died due to an opioid overdose that was assessed by the investigator as not related to investigational product.

Of the subjects who completed the protocol-defined treatment period, 1 subject (14.3%) in the IV-SC placebo group and 20 subjects (95.2%) in the MEDI-551 groups (5 subjects in the 30 mg IV; 3 subjects each in the 60 mg SC, 100 mg IV, and 300 mg SC; and 6 subjects in the 600 mg IV groups) entered the LTFU B-cell Recovery Period.

The duration of B-cell depletion remaining  $\geq 90\%$  from baseline and time to show a sign of recovery was dose dependent. In the 30, 100, and 600 mg IV dose cohorts, the median duration of  $\geq 90\%$  reduction was 149, 180, and 254 days, and time to show a sign of recovery was observed at Days 84, 163, and 258, respectively. The 60 and 300 mg SC dose cohorts, the median duration of  $\geq 90\%$  suppression was 100 and 211 days, respectively. The median time to reach the LLN was 250, 277 and 237 days for 30, 100, and 600 mg IV dose cohorts, respectively; and 196 days for 300 mg SC dose cohort.

**Figure 23: Sponsor Figure 11.4.1.1-1 Median Depletion and Recovery of CD20 B Cells following IV (x2) or SC Administration of inebilizumab**



## Safety

Two subjects in the placebo group and 1 subject in the MEDI-551 600 mg IV group had dose interruptions on Day 1. The infusion was interrupted for one subject after 43 minutes due to an AE of infusion related reaction (body itching); the infusion rate was reduced and the subject received the complete dose of investigational product. For the second subject, the infusion was interrupted after 19 minutes due to an AE of infusion related reaction (worsening blood pressure increased) and resumed with the subject receiving the full dose of investigational product.

One subject in the 30 mg inebilizumab IV group died due to an accidental opioid overdose with onset on Day 134. The event was assessed as not related to investigational product by the investigator.

TESAEs occurred in 1/7 subjects (14.3%) in the placebo group and 3/21 subjects (14.3%) in the total MEDI-551 group. One subject in the inebilizumab 300 mg SC group had a TESAE (pyrexia, regarded as injection related reaction) that was considered related to investigational product by the investigator.

In the placebo group, at the preferred term level, only TEAEs of multiple sclerosis relapse occurred in more than one subject. In the total inebilizumab group, the most frequent (incidence  $\geq 14\%$ ) TEAEs by preferred term were nasopharyngitis, upper respiratory infection, blood pressure increased, pyrexia, urinary tract infection, and urinary tract inflammation.

Two of 5 subjects (40.0%) in the IV placebo group and 6/15 subjects (40.0%) in the total IV inebilizumab group had TEAEs of infusion related reaction. All TEAEs of infusion related reaction were Grade 1 or Grade 2 in severity and assessed as related to investigational product by the investigator.

There were no subjects with anaphylaxis.

There were no cases of PML.

## **8.8. Additional Safety Explorations**

### **8.8.1. Human Carcinogenicity or Tumor Development**

One case of colon cancer was reported in the 120-day safety update. This is the only malignant neoplasm reported.

### **8.8.2. Human Reproduction and Pregnancy**

There were no pregnancies or other reproduction events in the data submitted.

### **8.8.3. Pediatrics and Assessment of Effects on Growth**

Subjects in the pediatric age group were not included.

### **8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There were no instances of overdose of inebilizumab. Abuse is not expected and therefore not addressed for this monoclonal antibody. There are no data at this time to assess the effect of discontinuation of inebilizumab on the occurrence of NMOSD relapses.

## **8.9. Safety in the Postmarket Setting**

### **8.9.1. Safety Concerns Identified Through Postmarket Experience**

Not applicable because inebilizumab is not approved for any indication at this time.

### 8.9.2. Expectations on Safety in the Postmarket Setting

Should inebilizumab be approved, it is likely that the safety profile of the drug will evolve as the number and duration of observations increase. The continued suppression of B-cell production and progressive reduction in key immunoglobulin levels may lead to an increasing incidence of infections.

### 8.9.3. Additional Safety Issues From Other Disciplines

There are no specific additional safety concerns based on the nonclinical or Clinical Pharmacology reviews up to the time of this review.

## 8.10. Integrated Assessment of Safety

### Any inebilizumab treatment population

The “any inebilizumab population” includes those 225 subjects treated with inebilizumab during the RCT or during the open label extension. Of those 225 subjects, 208 were anti-AQP4-IgG seropositive and 17 were seronegative.

#### Serious adverse events

The incidence of SAEs for the any inebilizumab population as of the time of submission is listed by SOC and preferred term in [Table 71](#). Events highlighted are those that occurred in subjects treated with inebilizumab after the end of the RCT and were, therefore not listed in [Table 46](#).

*Reviewer Comment: There is no apparent difference by anti-AQP4 IgG status for the incidence of SAEs for the any inebilizumab population. The Infections and Infestations SOC is the only one with any significant number of events and there are still too few in the seronegative group to make a valid comparison.*

**Table 70: SAEs by SOC and preferred term, any inebilizumab population**

| AEBODSYS                   | AEDECOD                          | N* | % of N = 225 |
|----------------------------|----------------------------------|----|--------------|
| Endocrine disorders        | Steroid withdrawal syndrome      | 1  | 0.44         |
| Eye disorders              | Cataract                         | 1  | 0.44         |
|                            | Vision blurred                   | 1  | 0.44         |
| Gastrointestinal disorders | Constipation                     | 1  | 0.44         |
|                            | Diarrhoea                        | 1  | 0.44         |
|                            | Gastrooesophageal reflux disease | 1  | 0.44         |
|                            | Umbilical hernia                 | 1  | 0.44         |

| AEBODSYS                                             | AEDECOD                                               | N* | % of N = 225 |
|------------------------------------------------------|-------------------------------------------------------|----|--------------|
| General disorders and administration site conditions | Pyrexia                                               | 1  | 0.44         |
| Hepatobiliary disorders                              | Cholangitis acute                                     | 1  | 0.44         |
|                                                      | Cholecystitis acute                                   | 1  | 0.44         |
|                                                      | Hepatic function abnormal                             | 1  | 0.44         |
|                                                      |                                                       |    |              |
| Infections and infestations                          | Appendicitis                                          | 1  | 0.44         |
|                                                      | Atypical pneumonia                                    | 1  | 0.44         |
|                                                      | Central nervous system infection                      | 1  | 0.44         |
|                                                      | Chorioretinitis                                       | 1  | 0.44         |
|                                                      | Herpes zoster                                         | 1  | 0.44         |
|                                                      | Myelitis                                              | 1  | 0.44         |
|                                                      | Pneumonia                                             | 2  | 0.89         |
|                                                      | Progressive multifocal leukoencephalopathy            | 1  | 0.44         |
|                                                      | Pyelonephritis chronic                                | 1  | 0.44         |
|                                                      | Renal abscess                                         | 1  | 0.44         |
|                                                      | Subcutaneous abscess                                  | 1  | 0.44         |
|                                                      | Urinary tract infection                               | 5  | 2.22         |
|                                                      |                                                       |    |              |
| Injury, poisoning and procedural complications       | Burns third degree                                    | 1  | 0.44         |
|                                                      | Foot fracture                                         | 1  | 0.44         |
|                                                      | Infusion related reaction                             | 1  | 0.44         |
| Investigations                                       | International normalised ratio increased              | 1  | 0.44         |
| Musculoskeletal and connective tissue disorders      | Arthralgia                                            | 1  | 0.44         |
|                                                      | Back pain                                             | 1  | 0.44         |
|                                                      | Musculoskeletal pain                                  | 1  | 0.44         |
|                                                      | Pain in extremity                                     | 1  | 0.44         |
| Nervous system disorders                             | Neuromyelitis optica spectrum disorder                | 3  | 1.33         |
|                                                      | Peripheral nerve palsy                                | 1  | 0.44         |
|                                                      | Post cardiac arrest syndrome                          | 1  | 0.44         |
| Psychiatric disorders                                | Delirium                                              | 1  | 0.44         |
|                                                      | Depression                                            | 1  | 0.44         |
| Respiratory, thoracic and mediastinal disorders      | Respiratory failure                                   | 1  | 0.44         |
| Skin and subcutaneous tissue disorders               | Drug reaction with eosinophilia and systemic symptoms | 1  | 0.44         |

Source: AESER\_Y Subset of ANL04FL\_Y Subset of ASTRFL\_Y Subset of ADAE By (USUBJID, AEDECOD, AEBODSYS) NUSUBJID By (AEBODSYS, AEDECOD).jmp

\*: N = NUSUBJID

**Reviewer Comment:** Subject (b) (6) had an event of DRESS syndrome starting on (b) (6) (study day 446 during the OLP) and ending on study day 446. The first dose of study drug was (b) (6) at the start of the OLP and the most recent dose of study drug was on (b) (6). Signs and symptoms of DRESS started 3 days after the start of carbamazepine for pain. This subject subsequently developed jaundice with elevated liver transaminases and bilirubin. The clinical course was complicated by skin abscesses that were positive for

*methicillin-resistant Staph aureus, treated with Vancomycin. The liver transaminases and bilirubin were improving at the time that the subject withdrew consent.*

At the time of the 120-day safety update, the only SAE of interest that had not occurred at the time of submission was a case of neutropenia (Subject (b) (6)). This event occurred after the data cut-off date but was included by the sponsor. The full narrative for this event is in Appendix 13.8.2.

*Reviewer Comment: This subject has preceding periods of neutropenia that did not result in discontinuation of the study drug. The event listed was the lowest neutrophil count and did result in drug discontinuation. There had been two previous episodes of "influenza" that resolved without discontinuation of the drug. With the possible exception those two events, the subject does not appear to have had consequences of the neutropenia.*

**Table 71: SAEs, by SOC and preferred term, any inebilizumab population, 120-day safety update.**

| AEBODSYS                                             | AEDECOD                          | N = 225 |      |
|------------------------------------------------------|----------------------------------|---------|------|
|                                                      |                                  | N*      | %    |
| Blood and lymphatic system disorders                 | Neutropenia                      | 1       | 0.44 |
| Endocrine disorders                                  | Steroid withdrawal syndrome      | 1       | 0.44 |
| Eye disorders                                        | Cataract                         | 1       | 0.44 |
|                                                      | Vision blurred                   | 1       | 0.44 |
| Gastrointestinal disorders                           | Constipation                     | 1       | 0.44 |
|                                                      | Diarrhoea                        | 1       | 0.44 |
|                                                      | Gastroesophageal reflux disease  | 1       | 0.44 |
|                                                      | Umbilical hernia                 | 1       | 0.44 |
| General disorders and administration site conditions | Pyrexia                          | 1       | 0.44 |
| Hepatobiliary disorders                              | Cholangitis acute                | 1       | 0.44 |
|                                                      | Cholecystitis acute              | 2       | 0.89 |
|                                                      | Hepatic function abnormal        | 1       | 0.44 |
| Infections and infestations                          | Appendicitis                     | 1       | 0.44 |
|                                                      | Atypical pneumonia               | 1       | 0.44 |
|                                                      | Bacteraemia                      | 1       | 0.44 |
|                                                      | Bronchiolitis                    | 1       | 0.44 |
|                                                      | Cellulitis                       | 1       | 0.44 |
|                                                      | Central nervous system infection | 1       | 0.44 |
|                                                      | Chorioretinitis                  | 1       | 0.44 |
|                                                      | Herpes zoster                    | 1       | 0.44 |
|                                                      | Intervertebral discitis          | 1       | 0.44 |
|                                                      | Pneumonia                        | 2       | 0.89 |

| AEBODSYS                                                            | AEDECOD                                               | N = 225 |      |
|---------------------------------------------------------------------|-------------------------------------------------------|---------|------|
|                                                                     |                                                       | N*      | %    |
|                                                                     | Progressive multifocal leukoencephalopathy            | 1       | 0.44 |
|                                                                     | Pyelonephritis chronic                                | 1       | 0.44 |
|                                                                     | Renal abscess                                         | 1       | 0.44 |
|                                                                     | Sinusitis                                             | 1       | 0.44 |
|                                                                     | Subcutaneous abscess                                  | 1       | 0.44 |
|                                                                     | Urinary tract infection                               | 7       | 3.11 |
| Injury, poisoning and procedural complications                      | Burns third degree                                    | 1       | 0.44 |
|                                                                     | Foot fracture                                         | 1       | 0.44 |
|                                                                     | Infusion related reaction                             | 1       | 0.44 |
| Investigations                                                      | International normalised ratio increased              | 1       | 0.44 |
| Musculoskeletal and connective tissue disorders                     | Arthralgia                                            | 1       | 0.44 |
|                                                                     | Back pain                                             | 1       | 0.44 |
|                                                                     | Musculoskeletal pain                                  | 1       | 0.44 |
|                                                                     | Pain in extremity                                     | 1       | 0.44 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Colon cancer stage III                                | 1       | 0.44 |
| Nervous system disorders                                            | Myelitis transverse**                                 | 1       | 0.44 |
|                                                                     | Neuromyelitis optica spectrum disorder                | 4       | 1.78 |
|                                                                     | Peripheral nerve palsy                                | 1       | 0.44 |
|                                                                     | Post cardiac arrest syndrome                          | 1       | 0.44 |
|                                                                     | Seizure                                               | 1       | 0.44 |
| Psychiatric disorders                                               | Delirium                                              | 1       | 0.44 |
|                                                                     | Depression                                            | 1       | 0.44 |
| Renal and urinary disorders                                         | Acute kidney injury                                   | 1       | 0.44 |
| Respiratory, thoracic and mediastinal disorders                     | Respiratory failure                                   | 1       | 0.44 |
| Skin and subcutaneous tissue disorders                              | Drug reaction with eosinophilia and systemic symptoms | 1       | 0.44 |

**Source:** AESER\_Y Subset of ANL04FL\_Y Subset of ADAE safety update By (USUBJID, AEDECOD, AEBODSYS) NUSUBJID By (AEBODSYS, AEDECOD).jmp

\*: N = NUSUBJID

\*\*: this event was listed as "myelitis" in the Infections SOC for the RCP and Any inebilizumab analyses

### Adverse Events

The most common adverse events in the any inebilizumab population ([Table 72](#)) did not differ significantly from those that occurred during the RCP ([Table 49](#)). At the time of the 120-day safety update the overall proportion of subjects with an AE and the number of events that occurred in 5% or more of the any inebilizumab population had increased as the period of observation increased ([Table 73](#)).

*Reviewer Comment: The types of events do not raise any new safety concerns.*

**Table 72: Adverse events, 5% or more of the any inebilizumab population**

| AEDECOD                           | N* | % (N=225) |
|-----------------------------------|----|-----------|
| Urinary tract infection           | 44 | 19.6      |
| Nasopharyngitis                   | 29 | 12.9      |
| Headache                          | 28 | 12.4      |
| Infusion related reaction         | 26 | 11.6      |
| Arthralgia                        | 23 | 10.2      |
| Back pain                         | 21 | 9.33      |
| Upper respiratory tract infection | 17 | 7.56      |
| Diarrhoea                         | 16 | 7.11      |
| Nausea                            | 16 | 7.11      |
| Cough                             | 15 | 6.67      |
| Influenza                         | 14 | 6.22      |
| Insomnia                          | 12 | 5.33      |

Source: ANL04FL\_Y Subset of ADAE By (USUBJID, AEDECOD) NUSUBJID By (AEDECOD).jmp

\*: N = NUSUBJID

**Table 73: Adverse events, 5% or more of the any inebilizumab population, 120-day safety update**

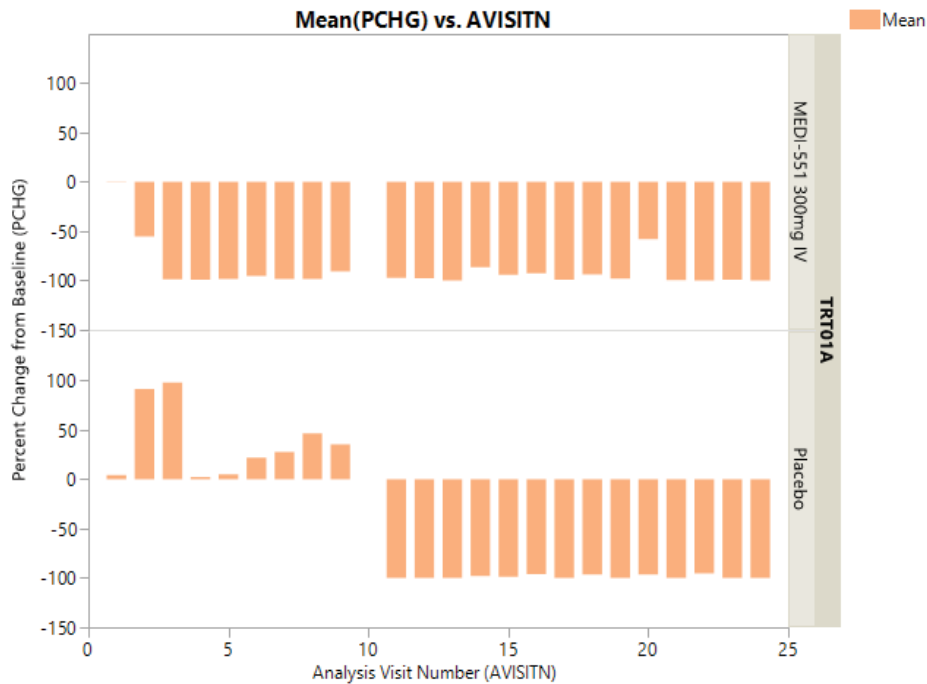
| AEDECOD                           | N* | % (N=225) |
|-----------------------------------|----|-----------|
| Urinary tract infection           | 50 | 22.2      |
| Nasopharyngitis                   | 37 | 16.4      |
| Headache                          | 31 | 13.8      |
| Back pain                         | 28 | 12.4      |
| Infusion related reaction         | 28 | 12.4      |
| Upper respiratory tract infection | 27 | 12        |
| Arthralgia                        | 26 | 11.6      |
| Cough                             | 18 | 8         |
| Diarrhoea                         | 18 | 8         |
| Nausea                            | 17 | 7.56      |
| Influenza                         | 16 | 7.11      |
| Insomnia                          | 15 | 6.67      |
| Pain in extremity                 | 14 | 6.22      |
| Constipation                      | 13 | 5.78      |
| Paraesthesia                      | 13 | 5.78      |
| Bronchitis                        | 12 | 5.33      |
| Eye pain                          | 12 | 5.33      |
| Fall                              | 12 | 5.33      |

Source: ANL04FL\_Y Subset of ANYMDFL\_Y Subset of ADAE safety update By (USUBJID, AEDECOD) NUSUBJID NUSUBJID By (AEDECOD).jmp

\*: N = NUSUBJID

## Laboratory results

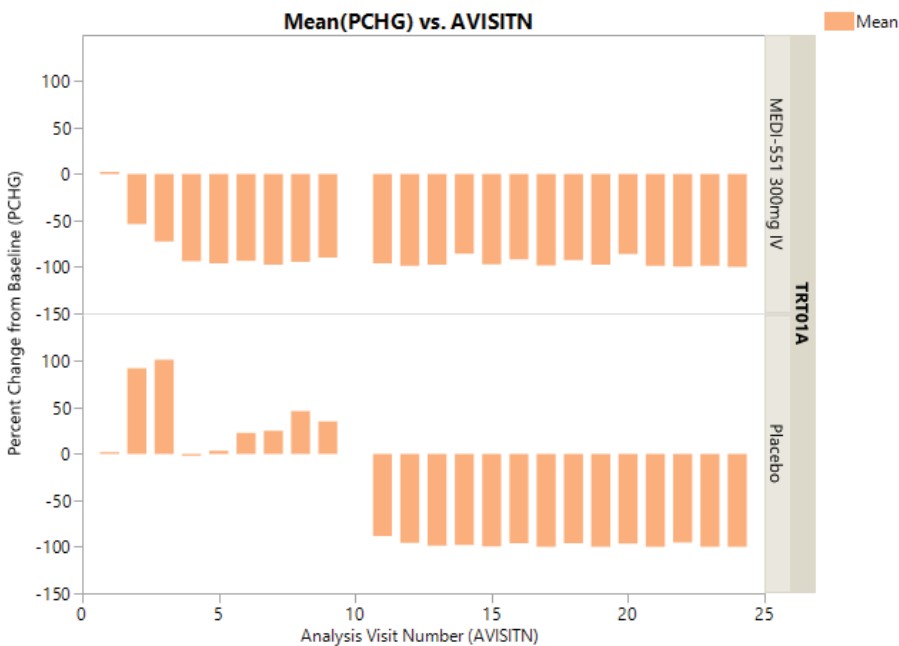
CD19+ cells during combined RCP and OLP



Source: PARAM\_CD19 Subset of EPOCH\_RCPandOLP Subset of ADLBFC.jmp

Exclude (b) (6): INEBILIZUMAB subject with 100% and 153,110% increase at Week 13 OLP visit (Day 92 OLP ADY 288)

The change in CD20+ cells were comparable to those for CD19+ cells.



Source: PARAM\_CD20 Subset of EPOCH\_RCPandOLP Subset of ADLBFC.jmp

Exclude (b) (6): INEBILIZUMAB subject with 149,646% increase at Week 13 OLP visit (Day 92 OLP ADY 288)

## **9. Advisory Committee Meeting and Other External Consultations**

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Advisory Committee not recommended

## **10. Labeling Recommendations**

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### **10.1. Prescription Drug Labeling**

Because approval will be limited to the population of NMOSD who are seropositive for the anti-AQP4 IgG antibody, the label should reflect the results for that population only. There are multiple other modifications recommended. See the final agreed labeling.

### **10.2. Nonprescription Drug Labeling – N/A**

## **11. Risk Evaluation and Mitigation Strategies (REMS)**

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A REMS is not recommended at this time.

## **12. Postmarketing Requirements and Commitments**

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A requirement to assess baseline immunoglobulin levels and to monitor immunoglobulin levels during treatment is recommended.

## **13. Appendices**

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### **13.1. References**

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### 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):** cd--ia-medi-551-1155

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         |                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: <u>4</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>4</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>5</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                                  |

|                                            |                                         |                                                                  |
|--------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Is an attachment provided with the reason: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |
|--------------------------------------------|-----------------------------------------|------------------------------------------------------------------|

### 13.3. NMOSD Attack Criteria

| Attack type    | Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Optic Neuritis | <ol style="list-style-type: none"> <li>Greater than 15-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in a previously affected eye and no other ophthalmological explanation</li> <li>At least 2-step drop c in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation</li> <li>At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye</li> <li>At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye</li> <li>At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye</li> <li>At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye</li> <li>At least 1-step drop d in CF to NLP from last visit as measured in a previously affected eye AND a new RAPD in affected eye</li> <li>At least 1-step drop d in CF to NLP from last visit as measured in a previously affected eye AND loss of a previously documented RAPD in fellow eye</li> <li>At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve f</li> <li>At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve f</li> <li>At least 1-step drop d in CF to NLP from last visit as measured in a previously affected eye <b>AND</b> a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve f</li> </ol> |
| Myelitis       | <ol style="list-style-type: none"> <li>At least 2-point worsening in 1 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit</li> <li>At least 1-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more</li> <li>At least 1-point worsening in 2 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit when the last visit score was 1 or greater AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord</li> <li>At least 0.5-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more <b>AND</b> a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Brainstem      | <ol style="list-style-type: none"> <li>Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting for greater than 48 hours AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem</li> <li>At least 2-point worsening in 1 or more of the relevant (brainstem, cerebellar) FSS compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Brain          | <ol style="list-style-type: none"> <li>At least 2-point worsening in 1 or more of the relevant (cerebral, sensory, pyramidal) FSS (with a score of 3 or more at the current visit) compared to last visit <b>AND</b> a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

CF = counting fingers; EDSS = Expanded Disability Severity Score; FSS = Functional System Scores; Gd = gadolinium; HM = hand motion; LP = light

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

perception; MRI = magnetic resonance imaging; NLP = no light perception; NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorders;

ON = optic neuritis; RAPD = relative afferent pupillary defect.

a The symptoms listed are examples and are not inclusive of all NMO/NMOSD symptoms.

b Four major areas of the body may be affected by an attack: the optic nerve, resulting in ON; the spinal cord, resulting in myelitis; the brainstem, resulting in a number of outcomes; and the brain.

c At least 2-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to HM, LP, or NLP; CF to LP or NLP; HM to NLP.

d At least 1-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP.

e Note: A 1-point change in a single FSS without a change in the EDSS, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and will not count as an attack per this protocol.

f Lesions seen in the optic chiasm also count towards these criteria.

#### 13.4. Schedule of Assessments – RCP

| Study Period                                                        | Randomized-controlled Period |     |                |     |     |     |     |     |        |
|---------------------------------------------------------------------|------------------------------|-----|----------------|-----|-----|-----|-----|-----|--------|
| Week                                                                | 0                            | 1   | 2              | 4   | 8   | 12  | 16  | 22  | 28/EDV |
| Day                                                                 | 1 <sup>h</sup>               | 8   | 15             | 29  | 57  | 85  | 113 | 155 | 197    |
| Visit Window                                                        |                              | ±1d | ±3d            | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d    |
| Procedure / Visit Number                                            | 2                            | 3   | 4              | 5   | 6   | 7   | 8   | 9   | 10     |
| Verify eligibility criteria                                         | X                            |     |                |     |     |     |     |     |        |
| SF-36v2 Health Survey <sup>a</sup>                                  | X                            |     |                |     |     | X   |     |     | X      |
| Pain NRS                                                            | X                            |     |                | X   | X   | X   | X   | X   | X      |
| Modified Rankin Scale                                               | X                            |     |                | X   | X   | X   | X   | X   | X      |
| Medical and disease history (including smoking and alcohol history) | X                            |     |                |     |     |     |     |     |        |
| C-SSRS ("Since Last Visit" version) <sup>g</sup>                    | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Physical/neurological examination                                   | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Body weight                                                         | X                            |     |                |     |     | X   |     |     | X      |
| Vital signs                                                         | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| ECG                                                                 | X                            |     |                |     |     |     |     |     | X      |
| <b>Collect blood for:</b>                                           |                              |     |                |     |     |     |     |     |        |
| Hematology and serum chemistry                                      | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| INEBILIZUMAB concentration (PK)                                     | X <sup>b</sup>               | X   | X <sup>b</sup> | X   | X   | X   | X   | X   | X      |
| INEBILIZUMAB ADA                                                    | X                            |     |                | X   |     | X   |     |     | X      |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

| Study Period                                                                        | Randomized-controlled Period |     |                |     |     |     |     |     |        |
|-------------------------------------------------------------------------------------|------------------------------|-----|----------------|-----|-----|-----|-----|-----|--------|
| Week                                                                                | 0                            | 1   | 2              | 4   | 8   | 12  | 16  | 22  | 28/EDV |
| Day                                                                                 | 1 <sup>h</sup>               | 8   | 15             | 29  | 57  | 85  | 113 | 155 | 197    |
| Visit Window                                                                        |                              | ±1d | ±3d            | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d    |
| Procedure / Visit Number                                                            | 2                            | 3   | 4              | 5   | 6   | 7   | 8   | 9   | 10     |
| Total Ig, IgM, IgG, IgA, IgE                                                        | -                            |     |                |     |     | X   |     |     | X      |
| Whole blood for flow cytometry (B-cell count and cell subsets)                      | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Serum for AQP4-IgG assay (titers)                                                   | X                            |     | X              | X   | X   | X   |     |     | X      |
| Whole blood for gene expression                                                     | X                            |     | X              | X   | X   | X   | X   |     | X      |
| Whole blood for DNA sample (optional)                                               | X                            |     |                |     |     |     |     |     |        |
| Serum for exploratory biomarkers                                                    | X                            |     | X              | X   | X   | X   | X   | X   | X      |
| Vaccination titers (tetanus) <sup>i</sup>                                           | X                            |     |                |     |     |     |     |     | X      |
| <b>Collect urine for:</b>                                                           |                              |     |                |     |     |     |     |     |        |
| Urine HCG (females with childbearing potential only) (pre-IV)                       | X                            |     | X              |     |     |     |     |     | X      |
| Urinalysis                                                                          | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Assess subject for new/worsening symptoms related to NMO/NMOSD <sup>d, e</sup>      | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Independent EDSS/FSS administration <sup>g</sup>                                    | X                            |     |                |     |     | X   |     |     | X      |
| Independent ophthalmology examination (high-/low-contrast visual acuity test, RAPD) | X                            |     |                |     |     | X   |     |     | X      |
| Neuroaxis MRI (including optic nerve)                                               |                              |     |                |     |     |     |     |     | X      |
| Randomize subjects in IVRS                                                          | X                            |     |                |     |     |     |     |     |        |
| <b>Investigational product administration</b>                                       | X                            |     | X <sup>j</sup> |     |     |     |     |     |        |
| Dispense/monitor low-dose steroids                                                  | X                            | X   | X              | X   |     |     |     |     |        |
| Assessment of AEs/SAEs (including infusion reactions)                               | X                            | X   | X              | X   | X   | X   | X   | X   | X      |
| Concomitant medications                                                             | X                            | X   | X              | X   | X   | X   | X   | X   | X      |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

| Study Period                                          | Randomized-controlled Period |     |     |     |     |     |     |     |        |
|-------------------------------------------------------|------------------------------|-----|-----|-----|-----|-----|-----|-----|--------|
| Week                                                  | 0                            | 1   | 2   | 4   | 8   | 12  | 16  | 22  | 28/EDV |
| Day                                                   | 1 <sup>h</sup>               | 8   | 15  | 29  | 57  | 85  | 113 | 155 | 197    |
| Visit Window                                          |                              | ±1d | ±3d | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d    |
| Procedure / Visit Number                              | 2                            | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10     |
| Dispense and review subject HCRU diaries <sup>f</sup> | X                            | X   | X   | X   | X   | X   | X   | X   | X      |
|                                                       |                              |     |     |     |     |     |     |     |        |

ADA = anti-drug antibody; AE = adverse event; AQP4-IgG = autoantibodies against aquaporin-4; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day(s)  
D/C = discontinuation; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EDV = Early Discontinuation Visit; FSS = Functional Systems  
Scores; HCG = human chorionic gonadotropin; HCRU = Healthcare Resource Utilization; Ig A/E/G/M = immunoglobulin A/E/G/M; IV = intravenous; IVRS =  
interactive voice response system; MRI = magnetic resonance imaging; NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorders; NRS =  
numeric rating scale; PK = pharmacokinetic; RAPD = relative afferent pupillary defect; RCP = Randomized-controlled Period; SAE = serious adverse event; SF-  
36v2 = Short Form-36 Health Survey, version 2

Note: All procedures to be performed prior to randomization.

- a SF-36v2 Health Survey 4-week recall to be used at all time points. The 1-week recall version will also be used for an attack.
- b Pharmacokinetic blood samples to be collected pre-dose and approximately 15 minutes post-dose (± 5 minutes) after completion of INEBILIZUMAB or placebo administration.
- c Urine HCG to be followed up to 26 weeks following discontinuation.
- d If a subject has an NMO/NMOSD attack prior to Day 1, and the subject has not been randomized, the visit should not continue. The subject should be treated for the attack as required, screen failed, and then reassessed for eligibility once the subject's condition is stable.
- e In the event that an NMO/NMOSD attack is suspected, procedures in Section 4.2.3 should be followed.
- f Subject diaries will be distributed to aid in subject recollection of HCRU events.
- g If the EDSS and the C-SSRS are performed by the same person, the EDSS must be done first.
- h If necessary, the randomization visit may be split over 2 days, in this case randomization and investigational product administration must occur on the second day.
- i Tetanus vaccine titers will be tested at Day 1 for all subjects. Subjects with a negative result will not continue to be tested. Subjects who test positive will continue to be tested at all specified vaccination titer timepoints.
- j In the event that the second dose of investigational product is delayed due to medical/safety reasons, dosing must be discussed with the medical monitor prior to administration of investigational product.

### 13.5. Schedule of Assessments – Attack Assessment Visit and Attack Follow-up Visit

#### Schedule of Assessments – Attack Assessment Visit

| Procedure                                                                                                              | Assessment Visit <sup>a</sup> |
|------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Pain NRS                                                                                                               | X                             |
| Vital signs                                                                                                            | X                             |
| Modified Rankin Scale                                                                                                  | X                             |
| Physical/neurological examination                                                                                      | X                             |
| <b>Collect blood for:</b>                                                                                              |                               |
| Hematology and serum chemistry                                                                                         | X                             |
| INEBILIZUMAB ADA                                                                                                       | X                             |
| Total Ig, IgM, IgG, IgA, IgE                                                                                           | X                             |
| Whole blood for flow cytometry (B-cell count and cell subsets)                                                         | X                             |
| Serum for AQP4-IgG assay (titers)                                                                                      | X                             |
| Whole blood for gene expression                                                                                        | X                             |
| Serum for exploratory biomarkers                                                                                       | X                             |
| Collect urine for urinalysis                                                                                           | X                             |
| <b>Procedures for determination of an NMO/NMOSD attack:</b>                                                            |                               |
| Independent ophthalmology examination (high-/low-contrast visual acuity test, RAPD assessment)                         | X                             |
| Independent EDSS/FSS administration <sup>c</sup>                                                                       | X                             |
| Neuroaxis MRI scan <sup>b</sup>                                                                                        | X                             |
| SF-36 (1-week recall version)                                                                                          | X                             |
| C-SSRS ("Since Last Visit" version) <sup>c</sup>                                                                       | X                             |
| ECG                                                                                                                    | X                             |
| Review data generated against protocol defined attack criteria and create a narrative of the Assessment Visit findings | X                             |
| Assessment of AEs and SAEs                                                                                             | X                             |
| Concomitant medications                                                                                                | X                             |
| Review subject diary entries                                                                                           | X                             |

ADA = anti-drug antibody; AE = adverse event; AQP4-IgG = autoantibodies against aquaporin-4; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FSS = Functional Systems Scores; Ig A/E/G/M = immunoglobulin A/E/G/M; MRI = magnetic resonance imaging; NMO/NMOSD = neuromyelitis optica/neuromyelitis spectrum disorders; NRS = numeric rating scale; RAPD = relative afferent pupillary defect; SAE = serious adverse event; SF-36 = Short Form-36 Health Survey

<sup>a</sup> Visit to be conducted within 72 hours of onset of report to site of new symptom(s) or worsening of an existing symptom(s) potentially related to NMO/NMOSD; visit may be conducted over 5 days.

<sup>b</sup> The MRI image/report is only reviewed by the Principal Investigator in the event it is required by the protocol-defined attack criteria.

<sup>c</sup> If the EDSS and the C-SSRS are performed by the same person, the EDSS must be done first.

#### Schedule of Events – Attack Follow-up Visit

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

| Procedure                                                                                      | Follow-up Assessment Visit <sup>a</sup>        |
|------------------------------------------------------------------------------------------------|------------------------------------------------|
| Visit Window                                                                                   | 28 days ( $\pm$ 7 days) After Assessment Visit |
| Pain NRS                                                                                       | X                                              |
| Vital signs                                                                                    | X                                              |
| Modified Rankin Scale                                                                          | X                                              |
| SF-36 Health Survey (1-week recall version)                                                    | X                                              |
| C-SSRS ("Since Last Visit" version) <sup>c</sup>                                               | X                                              |
| Physical/neurological examination                                                              | X                                              |
| <b>Collect blood for:</b>                                                                      |                                                |
| Hematology and serum chemistry                                                                 | X                                              |
| Whole blood for flow cytometry (B-cell count and cell subsets)                                 | X                                              |
| Serum for AQP4-IgG assay (titers)                                                              | X                                              |
| Collect urine for urinalysis                                                                   | X                                              |
| Independent ophthalmology examination (high-/low-contrast visual acuity test, RAPD assessment) | X <sup>b</sup>                                 |
| Independent EDSS/FSS administration                                                            | X <sup>b, c</sup>                              |
| Assessment of AEs and SAEs                                                                     | X                                              |
| Concomitant medications                                                                        | X                                              |

### 13.6. Schedule of Assessments during the Open Label Period

| Study Period                                                   | Open-label Period                                          |     |     |      |      |                  |                      |
|----------------------------------------------------------------|------------------------------------------------------------|-----|-----|------|------|------------------|----------------------|
| Week                                                           | 0                                                          | 2   | 4   | 13   | 26   | 39, then<br>Q26W | 52, then<br>Q26W/EDV |
| Day                                                            | 1                                                          | 15  | 29  | 92   | 183  | 274+             | 365+                 |
| Visit Window                                                   | (+ 14d from<br>Day 197 RCP<br>or +28d AC<br>Determination) | ±3d | ±3d | ±14d | ± 7d | ± 14d            | ±7d                  |
| Procedure/Visit Number                                         | 1                                                          | 2   | 3   | 4    | 5    | 6, 8,10, etc     | 7, 9, 11, etc        |
| Written informed consent                                       | X                                                          |     |     |      |      |                  |                      |
| SF-36v2 Health Survey                                          |                                                            |     |     | X    | X    | X                | X                    |
| Pain NRS                                                       |                                                            |     | X   | X    | X    | X                | X                    |
| Modified Rankin Scale                                          |                                                            |     | X   | X    | X    | X                | X                    |
| Physical/neurological examination                              | X <sup>a</sup>                                             | X   | X   | X    | X    | X                | X                    |
| C-SSRS ("Since Last Visit" version) <sup>h</sup>               | X <sup>a</sup>                                             | X   | X   | X    | X    | X                | X                    |
| Vital signs                                                    | X <sup>a</sup>                                             | X   | X   | X    | X    | X                | X                    |
| <b>Collect blood for:</b>                                      |                                                            |     |     |      |      |                  |                      |
| Hematology and serum chemistry                                 | X <sup>a</sup>                                             | X   | X   | X    | X    | X                | X                    |
| INEBILIZUMAB ADA                                               | X <sup>a</sup>                                             |     |     | X    | X    | X                | X                    |
| Total Ig, IgM, IgG, IgA, IgE                                   | X <sup>a</sup>                                             |     |     | X    | X    | X                | X                    |
| Whole blood for flow cytometry (B-cell count and cell subsets) |                                                            | X   | X   | X    | X    | X                | X                    |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

| Study Period                                                                                    | Open-label Period                                          |                |     |      |      |                  |                      |
|-------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------|-----|------|------|------------------|----------------------|
| Week                                                                                            | 0                                                          | 2              | 4   | 13   | 26   | 39, then<br>Q26W | 52, then<br>Q26W/EDV |
| Day                                                                                             | 1                                                          | 15             | 29  | 92   | 183  | 274+             | 365+                 |
| Visit Window                                                                                    | (+ 14d from<br>Day 197 RCP<br>or +28d AC<br>Determination) | ±3d            | ±3d | ±14d | ± 7d | ± 14d            | ±7d                  |
| Procedure/Visit Number                                                                          | 1                                                          | 2              | 3   | 4    | 5    | 6, 8,10, etc     | 7, 9, 11, etc        |
| Serum for AQP4-IgG assay (titers)                                                               | X <sup>a</sup>                                             |                | X   | X    | X    |                  | X                    |
| Whole blood for gene expression                                                                 |                                                            |                | X   | X    | X    |                  | X                    |
| Serum for exploratory biomarkers                                                                |                                                            | X              | X   | X    | X    | X                | X                    |
| Vaccination titers (tetanus) <sup>j</sup>                                                       |                                                            |                |     | X    | X    |                  | X                    |
| <b>Collect urine for:</b>                                                                       |                                                            |                |     |      |      |                  |                      |
| Urine HCG (females with childbearing potential only; pre-IV dose only)                          | X <sup>b</sup>                                             | X              |     |      | X    |                  | X                    |
| Urinalysis                                                                                      | X <sup>a</sup>                                             | X              | X   | X    | X    | X                | X                    |
| Assess subject for new/worsening symptoms related to NMO/NMOSD <sup>c</sup>                     | X <sup>b</sup>                                             | X              | X   | X    | X    | X                | X                    |
| Independent EDSS/FSS administration <sup>h</sup>                                                |                                                            |                |     | X    | X    | X                | X                    |
| Independent ophthalmology examination (high-/low- contrast visual acuity test, RAPD assessment) |                                                            |                |     | X    | X    | X                | X                    |
| Neuroaxis MRI (including optic nerve)                                                           | (X) <sup>d</sup>                                           |                |     |      |      |                  | X <sup>e</sup>       |
| <b>Investigational product administration</b>                                                   | X <sup>b</sup>                                             | X <sup>i</sup> |     |      | X    |                  | X <sup>g</sup>       |
| Assessment of AEs/SAEs (including infusion)                                                     | X <sup>b</sup>                                             | X              | X   | X    | X    | X                | X                    |
| Concomitant medications                                                                         | X <sup>b</sup>                                             | X              | X   | X    | X    | X                | X                    |
| Dispense and review subject HCRU diary entries <sup>f</sup>                                     | X <sup>b</sup>                                             | X              | X   | X    | X    | X                | X                    |

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

AC = Adjudication Committee; ADA = anti-drug antibody; AE = adverse event; AQP4-IgG = autoantibodies against aquaporin-4; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day(s); EDSS = Expanded Disability Status Scale; EDV = Early Discontinuation Visit; FSS = Functional Systems Scores; HCG = human chorionic gonadotropin; HCRU = Healthcare Resource Utilization; Ig A/E/G/M = immunoglobulin A/E/G/M; IV = intravenous; MRI = magnetic resonance imaging; NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorders; NRS = numeric rating scale; OLP = Open-label Period; Q26W = every 26 weeks; RAPD = relative afferent pupillary defect; RCP = Randomized-controlled Period; SAE = serious adverse event; SF-36v2 = Short Form-36 Health Survey, version 2

- a For subjects who enter the OLP prior to Day 197 of the RCP due to an AC-determined NMO/NMOSD attack and 14 days have elapsed since the Assessment Visit, all procedures listed for Day 1 should be repeated. For subjects completing Day 197 of the RCP, Day 1 of the OLP should be the same day; however, it may be delayed for up to 14 days and procedures do not need to be repeated.
- b Conduct for all subjects.
- c In the event that an NMO/NMOSD attack is suspected, procedures in Section 4.2.3 should be followed.
- d If the subject experienced an NMO/NMOSD attack during the RCP, any part of the neuroaxis MRI that was not done at the time of the Assessment Visit should be conducted at Day 1 of the OLP, otherwise it is not required.
- e An MRI will be conducted yearly.
- f Subject diaries will be distributed to aid in subject recollection of HCRU events.
- g If an EDV is being conducted, investigational product will not be given.
- h If the EDSS and the C-SSRS are performed by the same person, the EDSS must be done first.
- i In the event that the second dose of investigational product is delayed due to a medical/safety reason, dosing must be discussed with the medical monitor prior to administration of investigational product.
- j Tetanus vaccine titers will only be tested in the OLP for subjects who tested positive at Day 1 of the RCP.

### 13.7. Schedule of assessments during the Safety Follow-up Phase

|                                                                | Follow-up Period                                                                              |
|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Visit Number                                                   | Every 3 months for a total of 1 year after last dose of investigational product ( $\pm 14$ d) |
| Procedure/Study                                                |                                                                                               |
| Vital signs                                                    | X                                                                                             |
| C-SSRS ("Since Last Visit" version)                            | X                                                                                             |
| Whole blood for flow cytometry (B-cell count and cell subsets) | X                                                                                             |
| Total Ig, IgM, IgG, IgA, and IgE                               | X                                                                                             |
| Inebilizumab ADA                                               | X                                                                                             |
| Assessment of AEs/SAEs                                         | X                                                                                             |

ADA = anti-drug antibody; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); Ig A/E/G/M = immunoglobulin A/E/G/M; SAE = serious adverse event

### 13.8. Narratives

The narratives below represent selected verbatim excerpts from the narratives provided in Section 5.3.5.1 of the submission.

#### 13.8.1. SUBJECT (b) (6)

Preferred term = Hepatic function abnormal

Subject (b) (6) is a 44-year-old female who was randomized to receive inebilizumab. The subject received the first dose on (b) (6) and the last dose of inebilizumab prior to SAE was received on that same day. .... Relevant concomitant medications taken within 30 days of the SAE onset included carbamazepine, baclofen, Carsil (silymarin), Hepa Merz (L-ornithine, L-aspartate), Medrol (methylprednisolone), pantoprazole, tizanidine...

On (b) (6) the subject experienced grade 2 abnormal hepatic function. On an unspecified date, the subject was referred to a gastroenterologist because of known and persistent abnormal hepatic function. On (b) (6) the study drug administration was interrupted as a result of the abnormal hepatic function.

On (b) (6) (study day 223, 20 days after the last dose of inebilizumab) the subject was admitted to the gastroenterology ward due to persistent abnormal hepatic function. Physical examination revealed mild diffuse pain on palpation mostly on the left half of the abdomen. The liver and spleen did not appear enlarged. Laboratory results showed hemoglobin (HGB) 117.0 g/L, erythrocytes (RBC) 4.09, hematocrit (HCT) 35.7, thrombocytes (PLT) 232.0, prothrombin time (sec) 10.6, prothrombin time (%) 123.1, international normalized ratio (INR) 0.83, activated partial thromboplastin time (aPTT) 26.9, creatinine serum 65, bilirubin general 2.4, bilirubin

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

direct 0.7, aspartate aminotransferase (AST) serum 48, alanine aminotransferase (ALT) serum 55, gamma glutamyl transferase (GGT) serum 330, alkaline phosphatase 128.0, lipase 41.6, alpha-amylase 83, iron (Fe) 7.8, IBC 63.6, potassium 4.57 and sodium chloride 138.9 (units and reference ranges not provided). A urine analysis was positive for leucocytes. An abdominal ultrasound revealed non-homogenous, hyperechogenic parenchyma of the liver, no focal lesions; non-enlarged liver, pancreas, spleen, and kidneys; and a contracted gallbladder with lumen sludge.

On (b) (6) laboratory testing included: hepatitis B, hepatitis B core total antibodies, hepatitis C (anti-HCV) and hepatitis B surface antigen (HBsAg). Results were negative excluding viral etiology.

On (b) (6), laboratory results included AST 53, ALT 29, GGT 292. A gastroscopy showed hyperemic mucous membranes in the distal third, hiatal hernia, no changes in the distal esophagus and a small number of flat erosions in the herniated part of the stomach: hyperemic and edematous mucous membranes in rough relief and dull reflection, mucus membrane had coarse structure in part of the body, along the large curve, lightly spotted hyperemia in the antral region of the stomach. The pylorus was normal. Duodenum: hyperemic mucous membranes in rough relief, freely passable through jejunum. An antral biopsy was performed for *Helicobacter pylori*. Final diagnosis of the gastroscopy: hiatal hernia, erythema exudative and erosive chronic gastritis. The gastroenterologist's opinion is that obesity, dyslipidemia, high blood pressure and intake of carbamazepine can all contribute to the patient's condition of steatohepatitis. A slight drop in liver enzymes was observed as a result of treatment. On the same date, the subject was discharged from the hospital with home treatment medications Carsil Max and Panrazol (pantoprazole).

On (b) (6), LFTs showed ALT 74 U/L (6-34) and GGT 401 (4-49) U/L. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels during the study are graphed below. The patient's pre-randomization baseline ALT was 55-115 U/L (normal 6-34). The maximum ALT was 197 U/L on Day 8.

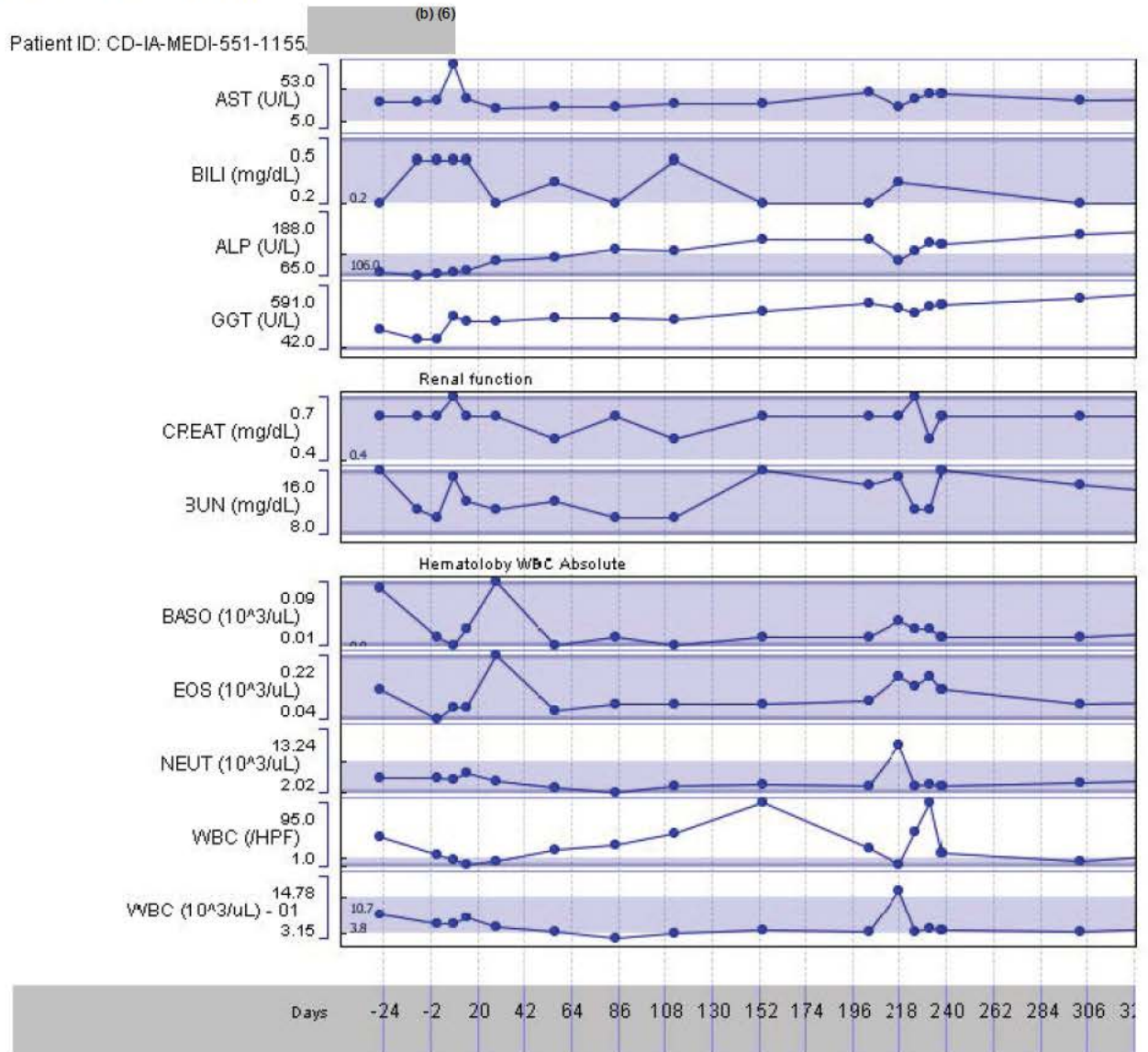
GPP from JReview

Patient ID: CD-IA-MEDI-551-1155/ (b) (6)  
Study: cd-ia-medi-551-1155  
Patient ID: CD-IA-MEDI-551-1155/ (b) (6)  
Description of Actual Arm: MEDI-551 300mg IV  
Study Site Identifier: 2000528  
Age: 43  
Country: BGR  
Sex: F  
Subject Death Flag:  
Race: WHITE  
Date/Time of First Study Treatment: (b) (6)

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

Date/Time of Last Study Treatment: (b) (6)  
Date/Time of Death:

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### 13.8.2. SUBJECT (b) (6)

Preferred Term: Neutropenia

Subject (b) (6) is a 46 year-old American Indian or Alaskan native female of Hispanic or Latino ethnicity who was randomized to the inebilizumab arm. On study day 117 (b) (6)

she experienced an AESI of neutropenia. The event was grade 1 severity, non-serious, and related to study drug per investigator. No specific treatment was given for the event. The event lasted 29 days and resolved. No other AEs occurred during this period of neutropenia. The subject's pre-treatment neutrophil counts were 1.38 and 1.52  $\times 10^3/\mu\text{L}$  (normal 1.96-7.23), which indicate the presence of grade 1 to grade 2 neutropenia per Common Terminology Criteria for Adverse Events (CTCAE) guidance prior to receiving study drug. A neutrophil count  $< 1.2 \times 10^3/\mu\text{L}$  at baseline was exclusionary.

On study day 117 (b) (6) the neutrophil count went to 0.98  $\times 10^3/\mu\text{L}$ , which is a grade 3 neutropenia per CTCAE guidance. Per protocol section **4.1.6 Discontinuation of Investigational Product**, investigational product dosing must be stopped if there is "grade 3 or higher neutropenia that does not improve to at least grade 2 within 5 days as agreed upon consultation with the medical monitor." A repeat neutrophil count performed on (b) (6) was 1.08  $\times 10^3/\mu\text{L}$ , which is grade 2 neutropenia. The subject was allowed to continue in the study because the lab test was obtained within 5 days of the site's awareness of the need to repeat the blood test.

*The following occurred after the date of data cutoff for the study but is included for completeness.* On study day 567 (b) (6) the neutrophil count went to 0.86  $\times 10^3/\mu\text{L}$ , which is grade 3 neutropenia. The site repeated the test which was 0.99  $\times 10^3/\mu\text{L}$  on (b) (6), which is grade 3 neutropenia. The subject was removed from the open-label period due to the grade 3 neutropenia that did not recover to grade 2; she continues to be observed in the safety follow-up period.

#### Opportunistic infection

Subject (b) (6) experienced two opportunistic infections of influenza. The first episode of influenza began on study day 375 (b) (6). The event was grade 1 severity, non-serious, and not related to study drug per investigator. No specific treatment was given. The event lasted 7 days and resolved. The second episode of influenza began on study day 438 (b) (6). The event was grade 1 severity, non-serious, and not related to study drug per investigator. No specific treatment was given. The event lasted 3 days and resolved.

#### 13.8.3. Subject (b) (6)

This 47-year old female who was randomized to receive inebilizumab. The subject received the first dose of inebilizumab on (b) (6) and the last dose of inebilizumab prior to SAE onset on (b) (6). The subject's relevant medical history included a hysterectomy, acute cystitis, depressive mood, muscle spasticity, allergic reactions to methylprednisolone and chlorpyramine. Concurrent medical condition includes herpes zoster and multiple sclerosis (MS) in remission. Relevant concomitant medications taken within 30 days of the SAE onset included acyclovir (oral), acyclovir (topical), amitriptyline, chlorithromycin and tizanidine.

SAE 1: Pneumonia

On (b) (6) (study day 665, 94 days after the last inebilizumab dose), the subject developed pneumonia which was grade 3 in intensity and required inpatient hospitalization. Chest x-ray was performed and the final diagnosis was pneumonia of the left lung. Repeat chest x-rays were done which showed improving left sided pneumonia. Blood testing was done and was found to be normal. The subject's treatment included intravenous cefazolin, Levoxa (levofloxacin) Medoclav (amoxicillin/clavulanic acid), Fromilid (clarithromycin), Degan (metoclopramide), Xyzal (levocetirizine dihydrochloride), methylprednisolone, Lactoflor (probiotic), vitamin C, Analgin (Metamizole Sodium), serum, and Amoxyclav (amoxicillin/clavulanate). On (b) (6) the subject was discharged to home in improved and afebrile condition, the subject was considered recovered from the event.

SAE 2: Pneumonia

On (b) (6), the subject contacted the investigators and reported that she had intermittent febrility for 2 weeks, every fourth day, with a temperature (T) of 37.5 degrees Celsius (C) axillary. She also experienced a mild cough, constant fatigue, and fever-like symptoms including sweating and unintentional weight loss. The subject was referred to a pulmonary disease unit as a computed tomography (CT) scan showed persistent morphological changes, and she was admitted to the hospital for further diagnostic clarification and treatment. An x-ray of the lungs showed a striped shadow in the right pericardial region and a dense pattern in the lungs indicated that the infection was in the initial stages of resorption. No focal changes in lung parenchyma. Treatment with intravenous (IV) Medocef (cefoperazone) and oral Tavipec (spicae aetheroleum) for bilateral pneumonia and paracetamol for febrility were initiated. On (b) (6), a bronchoscopy with lavage was performed for lung cancer, cytology and Pneumocystis jirovecii pneumonia. Visible bronchi, no changes, clear on both sides. The final diagnosis was bilateral pneumonia, grade 3 in severity. On (b) (6), the subject was discharged from the pulmonary ward of the hospital in improved condition. At the time of discharge, the treating pulmonologist prescribed (AZAX) azithromycin (oral) and Multilac until (b) (6). The decision was made to postpone her next visit to receive inebilizumab until her condition stabilized. On (b) (6), the subject recovered from bilateral pneumonia.

SAE 3: Pyrexia; Respiratory failure

On (b) (6) the subject experienced febrility, which was grade 2 in severity. On (b) (6) the subject developed respiratory failure which was grade 4 in severity and required hospitalization. The subject reported that on (b) (6) she experienced breathing difficulties, coughing, fatigue, dizziness, instability when walking, unintentional weight loss and febrility. On (b) (6), her condition worsened so she went to the emergency room (ER) and was subsequently admitted to the intensive care unit (ICU) for diagnosis and treatment. On the same date, a heart and lung X-ray showed pulmonary emphysema, peri-bronchial changes in perihilar and paracardiac regions and pleural adhesions base of left side of chest. On (b) (6), a sputum culture was positive for Streptococcus pneumoniae and on (b) (6), a sputum

culture was positive for Hemophilus influenzae and Candida albicans. A blood test for JC virus antibody was performed and was positive (index value of 2.41). On (b) (6), a head and neck MRI scan was performed which showed poorly defined, irregularly-shaped areas of changed signal intensity in the white matter in the left supratentorial, temporal and periventricular regions and the right anterior corpus callosum. The lesions had high signal intensity in T2 and FLAIR and were hypo intense in T1. The transverse size of the spinal cord was increased and its structure pathologically changed. The central canal was dilated. An irregularly shaped, poorly defined area of changed signal intensity was visible in the medulla spinalis from the dens axis to the upper edge of C6. On (b) (6) lymphocyte percentage was 8.8% (reference range 20-40). Treatment medications included intravenous (IV) sulperazon, IV fluconazole, IV amoxicillin/clavulanic acid, IV metoclopramide hydrochloride, IV omeprazole, IV piracetam, paracetamol, IV hydration, Fungolon (oral fluconazole), sulfamethoxazole/trimethoprim, acyclovir, biseptol, gerisan and oral metoclopramide hydrochloride. On (b) (6), the subject was afebrile and her breathing improved so she was transferred to the neurological ward for assessment of the main disease/condition. After testing, it was determined that no new neurological symptoms were detected. The subject was discharged on (b) (6) with improved condition (afebrile). The symptoms of general fatigue, cough, joint pain and stomach discomfort persisted.

On (b) (6), the subject was hospitalized to follow up on event respiratory failure and to evaluate immune status. Laboratory tests for immune function were performed and were notable for normal levels of IgG, IgA, IgM, C3, C4. Total CD3+ T lymphocytes were 493 (normal range 1,050-1,980; units not specified). CD19+ B cells were 0 (normal range 110-350, units not specified). Several specialists evaluated the patient. An unspecified specialist concluded “evidence of secondary immune deficiency. If there is no response to conventional antibacterial/antimycotic therapy, it will be appropriate to administer human immunoglobulin (no B-lymphocytes to respond to new/existing antigenic stimuli with specific antibody synthesis). The differential diagnosis based on blood count tests cannot rule out a systemic autoimmune disorder.” A specialist in acquired immune deficiencies concluded “this is a patient whose clinical laboratory tests results show clear evidence of B and T lymphocyte immunosuppression. The persistent bacterial, viral and mycotic infections are opportunistic, and their etiological treatment does not result a significant clinical effect until immunological recovery has been achieved. A clinical immunologist concluded “The immunological test shows absolute lymphopenia, mainly affecting B-lymphocytes, but also with significant effect on T-lymphocytes. The presence of peripheral immunoglobulins reflects the reserve of memory B cells and plasmocytes outside the peripheral blood flow. A clinical hematologist concluded “The probable cause of the deficiency is the treatment administered. The administration of immunoglobulins by i.v. would be appropriate to bring the infection under control. However, it will not result in lasting improvement in the deficiency.” A course of treatment with 15 g human immunoglobulins by i.v. was administered, which, by recommendation of an immunologist, will be administered monthly at the immune status checkup. The patient must be continuously monitored at the clinic.”

The subject was treated with IV glucose 10% solution, Ringer solution, Octagam 15 g IV,

Clinical Review  
Lawrence Rodichok MD  
BLA 761142  
Uplizna/inebilizumab

Biseptol, Fungolon, Acyclovir, and Gerisan. The outcome was improved and afebrile, but with persistent general fatigue, cough, joint pain, and stomach discomfort.

On [REDACTED] (b) (6), the event of respiratory failure was recovered and on [REDACTED] (b) (6), the event of febrility was resolved.

The action taken with the investigational product due to the SAE was not applicable as the subject elected to withdraw from the open label treatment period on [REDACTED] (b) (6) and will no longer be receiving inebilizumab.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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LAWRENCE D RODICHOK  
05/27/2020 09:07:31 AM

PAUL R LEE  
06/11/2020 01:37:10 AM  
I concur with the conclusions of this clinical review.