**Question 1:** Why was CD20 measured in N-Momentum when inebilizumab depletes CD19?

**Response 1 (old release):**

<h2>Understanding CD20 Measurement in N-MOmentum Trial with Inebilizumab Depletion of CD19</h2>  
<p>CD20 was measured in the N-MOmentum trial despite inebilizumab targeting CD19 due to the broader expression of CD19 compared to CD20, making CD19 a more attractive target for B cell-directed therapies in AQP4-IgG seropositive NMOSD [${1}].</p>  
  
<h3>Therapeutic Mechanism of Inebilizumab</h3><ul> <li>Inebilizumab, a humanized IgG1 targeting CD19, depletes B cells through antibody-dependent cellular cytotoxicity and phagocytosis, leading to effective B cell depletion [${3}].</li> <li>CD20 is expressed on pre-B cells, naive, mature, memory B cells, and some plasmablasts, while CD19 is a pan B cell marker present on pro-B cells, plasmablasts, and some plasma cells [${1}].</li></ul>  
<h3>N-MOmentum Trial Design and Efficacy</h3><ul> <li>The N-MOmentum trial for inebilizumab, a multicenter, double-blind, randomized placebo-controlled trial, demonstrated clear efficacy in reducing NMOSD relapses [${1}].</li> <li>Inebilizumab led to durable B cell and plasma cell depletion within a week, showcasing its therapeutic response in NMOSD [${2}].</li></ul>  
<h3>Mechanism of B Cell Depletion by Inebilizumab</h3><ul> <li>Inebilizumab binds to CD19 on B cells, resulting in effective depletion of peripheral B cells through antibody-dependent cellular cytolysis [${9}].</li> <li>The pharmacodynamic effect of inebilizumab on CD19+ B cells was rapid and robust, leading to sustained B cell depletion throughout the treatment period [${6}].</li></ul>  
<p>Therefore, despite inebilizumab targeting CD19, CD20 measurement in the N-MOmentum trial was crucial due to the broader expression of CD19 and the effective B cell depletion achieved by inebilizumab [${1}][${9}].</p>

**User Comment:**

The ask was essentially why was CD 20 measured instead of CD 19, as it is counter intuitive to measure something else than what you are targeting depleting. The answer had some good points, however the answer we were looking for is more so that for CD19+ B-cell counts, assays for CD20+ B cells are used because the presence of UPLIZNA interferes with CD19+ B-cell assay.   
  
Found in product monograph (should be added) and in-Br J Clin Pharmacol. 2022 Aug; 88(8): 3803–3812.  
Published online 2022 Apr 5. doi: 10.1111/bcp.15332  
PMCID: PMC9545531  
PMID: 35332558  
Pharmacodynamic modelling and exposure–response assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders  
Li Yan,corresponding author 1 Bing Wang, 2 Dewei She, 1 Ben Mitchell, 2 Ryan Criste, 2 Daniel Cimbora, 1 Eliezer Katz, 1 and William A. Rees 1

**Answer 1 in new response:**

**Rationale for Measuring CD20 in the N-Momentum Trial**

**Background on CD19 and CD20**

**CD19 and CD20 are both markers found on B cells, but they have different expression patterns and implications for B cell-targeted therapies:**

* **CD19** is a pan B cell marker, present on pro-B cells, plasmablasts, and some plasma cells. It is more selective for B cells compared to CD20, which can also be expressed on some T cells [[1A][4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
* **CD20** is found on pre-B cells, naive, mature, memory B cells, and some plasmablasts [[1A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).

**Therapeutic Mechanism of Inebilizumab**

Inebilizumab is a humanized IgG1 monoclonal antibody that targets CD19, leading to the depletion of B cells through antibody-dependent cellular cytotoxicity and phagocytosis [[4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2). Because CD19 is more broadly expressed than CD20, inebilizumab can target a wider range of B cells, including those not directly targeted by anti-CD20 therapies [[1A][4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).

**Measuring CD20 in the N-Momentum Trial**

**Despite inebilizumab targeting CD19, CD20 was measured in the N-Momentum trial for several reasons:**

1. **Understanding B Cell Depletion:**
   * Measuring CD20+ B cells helps to assess the overall depletion of B cells, as CD20 is a well-established marker for B cells in various stages of development [[1A][4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
   * The trial demonstrated that inebilizumab induced rapid and consistent depletion of CD20+ B cells starting at 8 days of treatment [[4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
2. **Correlation with Clinical Outcomes:**
   * The depth of B cell depletion, including CD20+ B cells, was correlated with clinical outcomes. Participants with deeper B cell depletion had lower annualized attack rates, fewer new/enlarging MRI lesions, and a trend towards decreased disability worsening [[2A][2C]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
   * This correlation helps to validate the efficacy of inebilizumab by showing that deeper depletion of B cells, including CD20+ B cells, is associated with better clinical outcomes [[2A][2C]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
3. **Comparative Analysis with Other Therapies:**
   * CD20 is a target for other B cell-depleting therapies, such as rituximab and ublituximab, which are used off-label for NMOSD [[2B]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2). Measuring CD20+ B cells allows for a comparative analysis of the efficacy and mechanism of action between inebilizumab and these other therapies [[2B]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
   * This comparison is crucial for understanding the unique benefits of targeting CD19 over CD20 and for positioning inebilizumab within the landscape of NMOSD treatments [[2B]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).

**Implications for Understanding Inebilizumab's Efficacy and Mechanism of Action**

**Measuring CD20 in the N-Momentum trial provides several insights:**

* **Validation of Broad B Cell Depletion:** It confirms that inebilizumab effectively depletes a broad range of B cells, including those expressing CD20, thereby supporting its mechanism of action [[4A]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
* **Clinical Correlation:** The correlation between CD20+ B cell depletion and improved clinical outcomes reinforces the therapeutic potential of inebilizumab in NMOSD [[2A][2C]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).
* **Comparative Efficacy:** It allows for a better understanding of how inebilizumab compares to other B cell-depleting therapies, highlighting its potential advantages in targeting a broader range of B cells [[2B]](https://companion-dev.amgen.com/c/66975cd55b5af9b3dc3901c2).

In conclusion, measuring CD20 in the N-Momentum trial, despite inebilizumab targeting CD19, provides a comprehensive understanding of B cell depletion, validates the therapeutic efficacy of inebilizumab, and offers valuable comparative insights with other B cell-targeted therapies.

**Details Required:**  
Feedback required about the comprehension and correctness of the present response

**Question 2:** What reference would you use to discuss switching a stable rituximab patient to Uplizna?

**Response 2 (old release)**:

<h2>Switching a Stable Rituximab Patient to Uplizna</h2>  
<p>To discuss switching a stable rituximab patient to Uplizna, the following key references can be utilized:</p>  
  
<h3>Prescribing Information</h3><p>The prescribing information for Uplizna (Inebilizumab-cdon) by Horizon provides essential details about the medication and its usage [${1}].</p>  
  
<h3>Research Studies</h3><p>Research studies such as the N-MOmentum trial have investigated the efficacy of Inebilizumab, the active ingredient in Uplizna, for the treatment of neuromyelitis optica spectrum disorder (NMOSD) [${2}].</p>  
  
<p>Additionally, a study by Flanagan et al. specifically explored the use of Inebilizumab in patients with NMOSD who had prior rituximab use, shedding light on the potential transition from rituximab to Uplizna in this patient population [${3}].</p>

**User Comment:**

While there isn't a single reference to answer this question, we were testing it to see if it would pull the data from slide decks or Standard Response letters that differentiate the CD19 B cell drug from CD20s. The comprehensive answer would include information about the glycoengineering of the product, the fact that its humanized, and that it targets CD19.

**Response 2 in new release:**

**Switching a Stable Rituximab Patient to Uplizna**

Switching a stable patient from rituximab to Uplizna (inebilizumab-cdon) involves several considerations, including efficacy, safety, and specific clinical guidelines. Below is a detailed discussion based on the provided context.

**Clinical Guidelines and Considerations**

**Efficacy and Mechanism of Action**

Both rituximab and Uplizna target B cells, but they do so through slightly different mechanisms:

* **Rituximab** targets CD20 on B cells, leading to their depletion [[3A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* **Uplizna** targets CD19, which is expressed on a broader range of B cells, including plasmablasts and some mature plasma cells. This broader targeting might offer enhanced efficacy in some patients [[3A][4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).

**Comparative Studies**

Several studies have examined the efficacy of Uplizna in patients previously treated with rituximab:

* **N-MOmentum Study**: This study included patients with a history of rituximab use. Among the 17 patients with prior rituximab therapy, 13 were randomized to receive inebilizumab. Notably, seven of these patients had experienced attacks during rituximab therapy, but none had attacks during inebilizumab treatment [[4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* **Flanagan et al. (2022)**: This study specifically looked at the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients with prior rituximab use. It found that inebilizumab was effective in this patient population [[1A][3A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).

**Safety Considerations**

Safety is a critical factor when switching therapies:

* **Infection Rates**: In the N-MOmentum trial, 94% of patients with prior rituximab use experienced infections compared to 70% without prior rituximab use. This suggests a higher risk of infections in patients switching from rituximab to inebilizumab [[4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* **Immunoglobulin Levels**: Patients with prior rituximab use had higher rates of low IgG levels, which could predispose them to infections [[4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).

**Specific Considerations for Switching**

* **Gap Between Therapies**: The N-MOmentum trial required a 6-month gap from rituximab before starting inebilizumab. This gap is essential to minimize overlapping immunosuppressive effects and reduce the risk of severe infections [[4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* **Cost**: Uplizna is significantly more expensive than rituximab. Uplizna costs approximately $393,000 for the first year and $262,000 per year thereafter, compared to rituximab's $18,000 per year. This cost difference may influence the decision to switch therapies [[3A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).

**Conclusion**

Switching a stable rituximab patient to Uplizna involves weighing the potential benefits of broader B cell targeting and possibly enhanced efficacy against the risks of higher infection rates and increased costs. Clinical guidelines recommend a 6-month gap between therapies to mitigate safety concerns. Real-world evidence and clinical trials, such as the N-MOmentum study, provide valuable insights into the efficacy and safety of this transition.

**References**

* Flanagan EP, Levy M, Katz E, et al. Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. Multiple Sclerosis and Related Disorders. 2022; 57:103352. doi:10.1016/j.msard.2021.103352 [[1A][3A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* N-MOmentum trial data on prior rituximab use and inebilizumab efficacy and safety [[4A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).
* Cost considerations and comparative efficacy of rituximab and inebilizumab [[3A]](https://companion-dev.amgen.com/c/66963a705b5af9b3dc39011a).

**Details required:**  
  
explicitly querying the info returned info on glycoengineering and humanization for the prompt: "*Which reference would you recommend for discussing the transition of a stable rituximab patient to Uplizna? Please include details about the product’s glycoengineering, its humanization status, and its targeting of CD19*"   
Requesting team to check the validity of the response gemerated from the prompt. Also, requesting relevant documents from medical affairs team

**Question 3:** 1 Summarize the advantages and disadvantages of approved therapies for NMOSD.

**Response 3 (old release):**

<h2>Advantages and Disadvantages of Approved Therapies for NMOSD</h2>  
<h3>Approved Therapeutic Options for NMOSD</h3><p>The neuro-immunological community now has several indicated agents for NMOSD therapy, each with advantages and disadvantages [${1}].</p>  
  
<h3>Eculizumab:</h3><ul> <li>Advantages:  
 <ul> <li>Does not affect the acquired immune system, preserving immunosurveillance [${1}].</li> <li>Immediate onset of action and persistent efficacy [${1}].</li> </ul> </li> <li>Disadvantages:  
 <ul> <li>Increases the risk of meningococcal infection by 1000 fold, requiring immunization [${1}].</li> <li>Requires frequent IV administration and is costly [${1}].</li> </ul> </li></ul>  
<h3>Inebilizumab:</h3><ul> <li>Advantages:  
 <ul> <li>Decreases B and plasmablast cell disease-inducing pathogenic antibody production [${1}].</li> <li>Allows self-administration [${3}].</li> </ul> </li> <li>Disadvantages:  
 <ul> <li>May cause immunosuppression and impede immunosurveillance [${1}].</li> <li>Similar to ocrelizumab, which depletes a wide range of lymphocytes [${1}].</li> </ul> </li></ul>  
<h3>Satralizumab:</h3><ul> <li>Advantages:  
 <ul> <li>Acts as an immunomodulator without significant loss of immunosurveillance [${3}].</li> <li>Requires continued administration for disease duration [${3}].</li> </ul> </li> <li>Disadvantages:  
 <ul> <li>Suffers from delayed onset of action [${3}].</li> <li>Considerable cost of treatment [${3}].</li> </ul> </li></ul>  
<p>Overall, each approved therapy for NMOSD has distinct advantages and disadvantages that need to be considered in treatment decisions [${1}][${3}].</p>

**User Comment:**

1. Does not focus on the major differences between the 3 therapies  
2. Does not include Ultomiris (Ravulizumab) amongst the novel FDA approved therapies  
3. Inaccurate information - Inebilizumab does NOT allow for self-administration.   
4. Inaccurate/Misleading information - Satralizumab does have a considerable cost of treatment but is amongst the cheapest of all FDA approved options, so it is misleading.

**Additional Context:**

Question was- Advantages and Disadvantages of Approved Therapies for NMOSD  
  
Answered povided- The neuro-immunological community now has several indicated agents for NMOSD therapy, each with distinct mechanisms of action, rapidity of onset, and long-term safety concerns [8].  
  
Eculizumab:  
Advantages:  
Preserves immunosurveillance and has an immediate onset of action with persistent efficacy [8].  
Disadvantages:  
Requires frequent IV administration and is costly [8].  
Increases the risk of meningococcal infection by 1000 fold, necessitating pre-treatment immunization [8].  
  
Inebilizumab:  
Advantages:  
Allows a slight decrease in relapse-free subjects and reduces pathogenic antibody production [8].  
Disadvantages:  
May cause immunosuppression and impede immunosurveillance by depleting a wide range of lymphocytes [8].  
Associated with hypo-gammaglobulinemia in 6% of cases [8].  
  
Satralizumab:  
Advantages:  
Immunomodulatory and allows self-administration [8].  
Disadvantages:  
Has a delayed onset of action [8].  
  
Overall, the choice of therapy for NMOSD should consider factors like efficacy, safety, accessibility, cost, and convenience, as each approved therapy has its unique advantages and disadvantages [10].  
  
Perhaps not a question the system is able to tease out. This answer would come from many different refreneces (curious why only reference number 8 was used to provide the limited answer?). A you can see fro the original user feedback, much of response was incorrect.

**Answer 3 in new release:**

**Advantages and Disadvantages of Approved Therapies for NMOSD**

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a severe autoimmune disorder characterized by recurrent episodes of optic neuritis and myelitis. The treatment landscape for NMOSD has evolved significantly, with several therapies now approved for use. Below is a balanced summary of the advantages and disadvantages of each approved therapy, focusing on their efficacy, safety profiles, and other relevant considerations.

**Eculizumab**

**Advantages:**

* **Efficacy:** Eculizumab, a C5 complement inhibitor, has demonstrated high efficacy in reducing NMOSD attacks. In the PREVENT trial, only 3% of patients treated with eculizumab experienced attacks compared to 43% in the placebo group [[3A][4A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Immediate Onset:** Eculizumab has an almost immediate onset of action and provides persistent efficacy [[1A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Immunosurveillance:** It does not affect the acquired immune system, thereby preserving immunosurveillance, which is crucial for recognizing and responding to foreign pathogens and cancerous cells [[1A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**Disadvantages:**

* **Infection Risk:** By blocking a compartment of the adaptive immune system, eculizumab increases the risk of meningococcal infection 1000-fold. Patients need to be immunized against Neisseria meningitidis before starting treatment [[1A][3A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Administration and Cost:** The therapy requires frequent intravenous (IV) administration and is associated with high costs [[1A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Limited Data on Monotherapy:** The PREVENT trial allowed the continuation of stable immunosuppressive therapy, making it difficult to assess the efficacy of eculizumab as a monotherapy [[2B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**Inebilizumab**

**Advantages:**

* **Efficacy:** Inebilizumab, an anti-CD19 monoclonal antibody, has shown efficacy in reducing NMOSD attacks and disability progression. It decreases B and plasmablast cell disease-inducing pathogenic antibody production [[1A][2B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Relapse Reduction:** In the N-MOmentum trial, inebilizumab significantly reduced relapse rates compared to placebo [[2B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**Disadvantages:**

* **Immunosuppression:** Inebilizumab causes immunosuppression by depleting a wide range of lymphocytes from the B-cell lineage, which may impede immunosurveillance and increase the risk of infections [[1A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Cancer Surveillance:** There is a potential for decreased cancer surveillance similar to ocrelizumab, with a 6% incidence of hypo-gammaglobulinemia [[1A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Limited Data on Seronegative Patients:** The efficacy in AQP4-IgG seronegative patients is not well established, as the trials were underpowered to assess this subgroup [[4B][5A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**Satralizumab**

**Advantages:**

* **Efficacy:** Satralizumab, an anti-IL-6 receptor monoclonal antibody, has demonstrated efficacy in reducing NMOSD attacks. In the SAkuraStar trial, it significantly reduced relapse rates compared to placebo [[2A][4A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Safety Profile:** Satralizumab has an acceptable safety profile and can be administered subcutaneously, offering convenience over IV administration [[2B][4B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**Disadvantages:**

* **Limited Data on Disability Progression:** While effective in reducing relapses, satralizumab's impact on long-term disability progression is less clear [[4B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Seronegative Patients:** Similar to inebilizumab, the efficacy in AQP4-IgG seronegative patients is not well established [[4B][5A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

**General Considerations**

* **Combination Therapy:** The safety data for NMOSD treatment trials that allowed for concomitant immunosuppression appear reassuring, but the benefits of combination therapy over monotherapy are not yet clear [[5A]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Individualized Treatment:** Choice of therapy should consider factors such as frequency and route of administration, side effect profiles, cost, and individual patient factors like age, comorbidities, and pregnancy plans [[2B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).
* **Long-term Safety:** Long-term safety monitoring is essential as these new medications become more widely used [[2B]](https://companion-dev.amgen.com/c/669630445b5af9b3dc3900ea).

In summary, while eculizumab, inebilizumab, and satralizumab offer significant benefits in reducing NMOSD attacks, each therapy comes with its own set of disadvantages, particularly concerning infection risks and the need for frequent administration. The choice of therapy should be individualized based on patient-specific factors and the evolving understanding of these treatments' long-term safety and efficacy profiles.

**Details required:**

1. Info on Ultomoris not present in the response. On prompting if Ultomoris is FDA aprroved for NMOSD treatmnt, response says it is not yet approved  
("FDA Approval Status  
As of the latest information available, ravulizumab (Ultomiris) has not yet received FDA approval for the treatment of NMOSD. While it has shown promise in clinical trials and has been approved for other conditions such as paroxysmal nocturnal hemoglobinuria (PNH), its use for NMOSD is still under investigation [3A][6A].") Requesting med affairs team to check this info  
  
2. Answer is referring multiple sources to come up with pros and cons. Need info of the document cited [8] (in the “additional context” section) for further analysis

**Question 4:** What is the dropout rate for patients enrolled in N-MOmentum?

**Response 4:**

<h2>Dropout Rate for Patients Enrolled in N-MOmentum Study</h2>  
<p>The N-MOmentum study, a multi-center, double-blind, randomized, placebo-controlled phase II/III trial, enrolled 230 patients with neuromyelitis optica spectrum disorder (NMOSD) [${3}].</p>  
  
<h3>Study Design and Patient Enrollment</h3><ul> <li>The study randomized participants in a 3:1 ratio to receive either intravenous inebilizumab 300 mg or placebo on days 1 and 15 [${3}].</li> <li>All patients received prednisone 20 mg daily for the first 14 days as prophylaxis against an NMOSD attack after the first dose of inebilizumab [${4}].</li> <li>The study included both AQP4-IgG seropositive and seronegative NMOSD patients, with no preplanned recruitment targets based on AQP4-IgG serostatus [${3}].</li></ul>  
<h3>Outcome Measures and Study Endpoints</h3><ul> <li>The primary endpoint of the N-MOmentum study was the time to an NMOSD attack as determined by an adjudication committee on or before day 197 [${3}].</li> <li>Disability outcomes were assessed using the Expanded Disability Status Scale (EDSS) and the modified Rankin Scale (mRS) scores [${5}].</li></ul>  
<h3>Treatment-Emergent Adverse Events</h3><ul> <li>During the study, treatment-emergent adverse events were reported in 72% of patients receiving inebilizumab and 73% of patients receiving placebo [${8}].</li></ul>  
<p>The N-MOmentum study provided valuable insights into the safety and efficacy of inebilizumab in individuals with NMOSD, capturing 730 person-years of exposure to the drug [${9}].</p>

**User Comment:**

It is accurate... but in no way answers the question asked. (Interestingly, some of this data was missing from another of my questions, where it was needed.) Figure 1 in the EoS manuscript addresses this question (Cree 2024 Lancet Neurol)

**Additional Context:**

Please see original user feedback- End of Study paper, table 1

**Answer 4 in new response:**

**Dropout Rate for Patients Enrolled in N-MOmentum**

The N-MOmentum trial was a multicenter, double-blind, randomized, placebo-controlled phase II/III study designed to evaluate the efficacy and safety of inebilizumab in patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) [[1A][5A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192). The trial included 230 patients, with 174 randomized to receive inebilizumab and 56 to receive placebo [[5A][6A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).

**Dropout Rate and Patient Retention**

The dropout rate for the N-MOmentum trial is not explicitly stated in the provided context. However, several key points regarding patient retention and the structure of the trial can be inferred:

1. **Randomized Control Period (RCP):**
   * Patients were randomized in a 3:1 ratio to receive either inebilizumab or placebo on days 1 and 15 [[1A][6A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
   * The RCP lasted up to 28 weeks or until an adjudicated attack occurred, at which point patients could transition to the open-label extension (OLE) phase [[6A][7A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
2. **Open-Label Extension (OLE):**
   * Patients who completed the RCP were eligible to enroll in the OLE phase, where all participants received inebilizumab [[1A][4A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
   * The OLE phase aimed to maintain B-cell depletion with inebilizumab 300 mg administered every 26 weeks [[4A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
3. **Study Termination:**
   * The study was terminated early by the data monitoring committee due to robust demonstration of efficacy and >99% statistical power, before reaching the target of 252 participants and 67 adjudicated attacks [[4A][7A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).

**Reasons for Dropout**

While specific dropout reasons are not detailed in the provided context, several factors that could influence patient retention in clinical trials like N-MOmentum include:

* **Adverse Events:** The adverse event profile was similar between AQP4-IgG seronegative and seropositive patients, suggesting that adverse events were managed consistently across patient groups [[2A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
* **Eligibility Criteria:** A significant number of potential participants were deemed ineligible due to stringent diagnostic criteria, particularly among AQP4-IgG seronegative patients [[3A][4A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).
* **Study Design:** The trial's design included measures to minimize dropout, such as transitioning placebo patients to inebilizumab upon experiencing an NMOSD attack and conducting an interim futility analysis to ensure efficacy [[7A]](https://companion-dev.amgen.com/c/6697172d5b5af9b3dc390192).

**Conclusion**

The N-MOmentum trial's dropout rate is not explicitly provided in the context. However, the trial's design and early termination due to efficacy suggest a robust patient retention strategy. Factors such as adverse events, stringent eligibility criteria, and the transition to an open-label extension phase likely influenced patient retention and dropout rates.

**Details required:**  
1. Reference needed, of the question, where the info from the present response had appeared, for further analysis  
2. Did not get reference to the "additional context" comment, in context to the question

**Question 5:** Discuss the use of steroids in NMOSD?

**Response 5:** <h2>Use of Steroids in Neuromyelitis Optica Spectrum Disorder (NMOSD)</h2>  
<p>Steroids play a crucial role in the management of acute relapses in NMOSD [${4}].</p>  
  
<h3>Traditional Immunosuppressive Treatment</h3><ul> <li>Azathioprine or mycophenolate mofetil, combined with low-dose corticosteroids, are commonly used in the treatment of NMOSD [${2}].</li> <li>Azathioprine, a prodrug of 6-mercaptopurine, inhibits purine synthesis and lymphocyte proliferation, showing positive results in NMOSD patients [${2}].</li> <li>Retrospective case series have demonstrated the efficacy of azathioprine in reducing annualized relapse rates and improving Expanded Disability Status Scale scores in NMOSD patients [${2}].</li> <li>Recent studies have shown that azathioprine is inferior to rituximab and tocilizumab in reducing relapses and disability progression in head-to-head comparisons [${2}].</li></ul>  
<h3>Specific Therapies</h3><ul> <li>Low-dose oral glucocorticoids are used to suppress the immune system in NMOSD patients, particularly in those who are AQP4-IgG-negative or have concomitant autoimmune diseases [${5}].</li> <li>Glucocorticoids are also used as a bridge therapy after an attack until the full effect of subsequent immunotherapy is achieved [${5}].</li> <li>Studies have reported the safe and effective use of azathioprine combined with low-dose glucocorticoids in Chinese patients with AQP4-IgG-positive NMOSD [${5}].</li> <li>Long-term use of glucocorticoids is associated with various side effects, including infections, diabetes mellitus, weight gain, Cushing's syndrome, and osteoporosis [${5}].</li></ul>  
<p>Overall, steroids, in combination with other immunosuppressive agents, are integral in managing acute relapses and long-term maintenance therapy in NMOSD [${6}].</p>

**User Comment:**

This response addresses the use of steroids in this disease rather than in the N-MOmentum trial. I don't love the question becasue I don't know if it is asking about use of steroids for acute attacks, or if it is referring to standard concomitant use/the taper given during the first several weeks of the trial. Assuming both, these are both outlined in bot hte study protocol and in the Lancet 2019.

**Additional Context:**

Question is too broad- this response was generally correct as the ask was not specific to one study. However, the responses provided are a bit misleading with regard to points outlined. Example- with regard to long term glucocorticsteroid use, the answer was out of context- should have included the fact that this reccomendation is usually only reserved for people in countries where biologics are not available.- Kümpfel, T et al. NEMOS dx and treatment recommendations. 2024 Jrl Neurol.pdf p.145   
  
Even when asking specifically for NMOmentum steroid use, the results are inconsistant. First snswer is clear that steroids are a taper, second reference states it is part of the regimine.

**Answer 5 in new release:**

**The Role of Steroids in NMOSD**

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a severe autoimmune condition characterized by relapses that can lead to significant neurological damage. Steroids play a crucial role in both the acute management and long-term treatment of NMOSD. This response provides a detailed overview of the use of steroids in NMOSD, including their efficacy, common protocols, potential side effects, and considerations for long-term management.

**Efficacy of Steroids in NMOSD**

Steroids are highly effective in managing acute relapses of NMOSD. The primary goal of steroid treatment is to curtail active inflammation, hasten recovery, and limit irreversible damage. High-dose intravenous (IV) methylprednisolone is the mainstay of acute treatment, typically administered at 1000 mg for 3-5 days [[1B][6A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b). This regimen has been shown to significantly reduce inflammation and improve clinical outcomes during acute attacks.

**Common Protocols for Steroid Use**

**Acute Management**

* **High-Dose IV Methylprednisolone:** Administered at 1000 mg daily for 3-5 days [[1B][6A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Oral Steroid Taper:** In severe cases, an oral steroid taper following IV steroids is recommended, although there is limited data on this practice [[1B]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Combination with Other Therapies**

* **Plasmapheresis (PLEX):** In refractory cases, plasmapheresis can be used in conjunction with steroids to target both cellular and humoral immune responses. Steroids should be administered following a PLEX session to ensure minimal removal of the steroid dose [[1B]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Add-On Therapies:** Steroids are often used as add-on therapies with other immunosuppressive agents such as azathioprine or mycophenolate mofetil [[2A][4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Potential Side Effects of Steroids**

Long-term use of steroids is associated with several side effects, including:

* **Infections:** Increased susceptibility to infections due to immunosuppression [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Metabolic Effects:** Diabetes mellitus, weight gain, and Cushing's syndrome [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Bone Health:** Osteoporosis and increased risk of fractures [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Other Effects:** Hypertension, mood changes, and gastrointestinal issues [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Considerations for Long-Term Management**

**Maintenance Therapy**

* **Low-Dose Glucocorticoids:** Low-dose oral glucocorticoids (5-15 mg) are used long-term in some NMOSD patients, particularly those who are AQP4-IgG-negative or have concomitant autoimmune diseases. This approach helps prevent attacks, although rapid tapering and doses below 10 mg/day are associated with a higher likelihood of relapse [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Bridging Therapy:** Prolonged oral methylprednisolone therapy is sometimes used to 'bridge' patients until the full effect of subsequent immunomodulatory or immunosuppressive treatment is achieved [[6A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Monitoring and Adjustments**

* **Tapering:** There are no controlled data on the optimal timing for tapering and stopping add-on glucocorticoid therapy. However, a daily prednisolone dose of 7.5 mg or less should ideally be achieved if used as a long-term treatment to minimize side effects [[4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).
* **Combination with Other Immunosuppressants:** Steroids are often combined with other immunosuppressive agents such as azathioprine or mycophenolate mofetil to enhance efficacy and reduce relapse rates [[2A][4A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Recent Clinical Guidelines and Studies**

Recent studies and clinical guidelines emphasize the importance of aggressive management of acute relapses and the use of long-term preventative immunosuppressive therapies. The use of high-dose IV methylprednisolone remains a cornerstone of acute management, while low-dose glucocorticoids are recommended for maintenance therapy in specific patient populations [[1B][4A][6A]](https://companion-dev.amgen.com/c/66970c015b5af9b3dc39017b).

**Conclusion**

Steroids are a critical component in the management of NMOSD, particularly for acute relapses. While highly effective, their long-term use requires careful monitoring and management to mitigate potential side effects. Combining steroids with other immunosuppressive agents can enhance treatment efficacy and reduce relapse rates, making them a vital part of the therapeutic arsenal against NMOSD.

**Details required:**

In points regarding glucocorticsteroid, info on recommendation being usually reserved for people in countries where biologics are not currently available is not present  
  
Requiring feedback from the med affairs team, with the new answer generated, and with specific prompts for the required studies

**Question 6:** Discuss broad immune reconstitution in NMSOD.

**Response 6 (old release):**

<h2>Immune Reconstitution in Neuromyelitis Optica Spectrum Disorder (NMOSD)</h2>  
<p>Neuromyelitis Optica spectrum disorder (NMOSD) is an inflammatory, immune-mediated, and demyelinating disorder of the central nervous system characterized by episodes of optic neuritis and transverse myelitis [${2}].</p>  
  
<h3>Current Treatment Approaches</h3><p>Traditional immunosuppressive and B-cell depletion therapies are the standard treatments for NMOSD, with Azathioprine recommended as a first-line treatment and Mycophenolate Mofetil as a second-line option [${2}].</p>  
<p>Rituximab has been proposed as a first-line maintenance treatment for NMOSD, showing efficacy in reducing relapse frequency and disability [${2}].</p>  
<p>Tocilizumab, recommended as a third-line therapy, has demonstrated effectiveness in patients who did not respond to other treatments [${2}].</p>  
  
<h3>Novel Therapeutic Approaches</h3><p>Recent studies have introduced mechanism-based drugs for NMOSD, including monoclonal antibodies such as eculizumab, satralizumab, inebilizumab, and rituximab [${4}].</p>  
<p>These monoclonal antibodies have shown promising results in prolonging the time to first relapse and preventing disability accrual in NMOSD patients [${4}].</p>  
  
<h3>Future Directions</h3><p>Research is ongoing to evaluate the safety and efficacy of monoclonal antibodies in NMOSD, with a focus on preventing relapses and improving clinical outcomes [${3}].</p>  
<p>These novel therapeutic approaches offer hope for patients with NMOSD by targeting specific mechanisms of the disease and potentially improving long-term treatment outcomes [${5}].</p>

**User Comment:**

This answer was no where near accurate and was not even up-to-date on current therapies for NMOSD. Also, the answer had nothing to do with immune reconstitution in NMOSD.

**Additional Context:** There really shoudlnt be an answer, thereapies in NMO do not reconsitiute immune system.

**Answer 6 in new response:**

**Broad Immune Reconstitution in NMOSD**

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare, chronic, autoimmune, inflammatory disorder of the central nervous system (CNS) characterized by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis [[3A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b). The disease is primarily mediated by the binding of aquaporin-4 (AQP4) antibodies, leading to severe inflammatory responses and subsequent neural damage [[5A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b). Broad immune reconstitution in NMOSD involves various therapeutic strategies aimed at modulating or resetting the immune system to prevent relapses and manage symptoms.

**Mechanisms of Immune Reconstitution**

1. **Autologous Hematopoietic Stem Cell Transplantation (AHSCT):**
   * **Mechanism:** AHSCT involves harvesting the patient's own hematopoietic stem cells, followed by high-dose immunosuppressive therapy to eliminate the existing immune system. The harvested stem cells are then reintroduced to regenerate a new, potentially less autoreactive immune system [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **Outcomes:** AHSCT has shown promise in preventing disease progression and reducing relapses in NMOSD. It is considered a potential therapeutic option, especially for patients with severe breakthrough disease after other disease-modifying therapies (DMTs) [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
2. **Monoclonal Antibodies:**
   * **Eculizumab:** This drug targets the complement system, specifically inhibiting the complement protein C5, which plays a crucial role in the inflammatory cascade triggered by AQP4 antibodies [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Advantages:** Eculizumab preserves immunosurveillance, has an immediate onset of action, and demonstrates persistent efficacy [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Drawbacks:** Frequent intravenous administration and high cost are significant limitations [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **Inebilizumab:** This monoclonal antibody targets CD19 on B cells, leading to the depletion of B cells and plasmablasts, thereby reducing the production of pathogenic antibodies [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Advantages:** Inebilizumab decreases relapse rates over time [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Drawbacks:** It may cause immunosuppression, posing a risk of infections [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **Satralizumab:** This drug targets the interleukin-6 (IL-6) receptor, modulating the immune response [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Advantages:** Satralizumab can be self-administered and has a good safety profile [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
     + **Drawbacks:** It has a delayed onset of action compared to other therapies [[1A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).

**Clinical Studies and Data**

1. **Eculizumab:**
   * **Clinical Trials:** Eculizumab has been tested in both open-label pilot studies and randomized controlled trials (RCTs), showing promising results in reducing relapse rates and improving clinical outcomes in NMOSD patients [[5A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **FDA Approval:** Eculizumab was approved by the FDA in June 2019 for the treatment of AQP4-IgG-positive NMOSD [[4A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
2. **Inebilizumab:**
   * **Clinical Trials:** Inebilizumab was evaluated in a double-blind, randomized placebo-controlled phase II/III trial, demonstrating significant efficacy in preventing relapses [[5A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **FDA Approval:** Inebilizumab received FDA approval in June 2020 for NMOSD treatment [[4A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
3. **Satralizumab:**
   * **Clinical Trials:** Satralizumab has shown efficacy and a good safety profile in multiple clinical studies, including phase III trials, for relapse prevention in NMOSD patients [[5A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).
   * **FDA Approval:** Satralizumab was approved by the FDA in August 2020 [[4A]](https://companion-dev.amgen.com/c/6697892a5b5af9b3dc39021b).

**Conclusion**

Broad immune reconstitution in NMOSD involves a multifaceted approach, including AHSCT and the use of monoclonal antibodies like eculizumab, inebilizumab, and satralizumab. These therapies aim to reset or modulate the immune system to prevent relapses and manage symptoms effectively. While each treatment has its advantages and drawbacks, ongoing clinical studies and real-world data continue to refine their use and improve outcomes for NMOSD patients.

**Details required:**

Require feedback from med affairs team about the accuracy and relevance of the response in this release

**Question 7:** 2. Are there any specific medical conditions that often coexist with NMOSD?

**Response 7 (old release)**

<h2>Medical Conditions Coexisting with NMOSD</h2>  
<p>Neuromyelitis optica spectrum disorder (NMOSD) is frequently associated with various antibody-mediated autoimmune disorders, including myasthenia gravis, lupus, and Sjogren syndrome among others [${1}].</p>  
  
<ul> <li>Myasthenia gravis is reported to coexist more frequently than expected with NMOSD, often occurring several years after the initial myasthenia diagnosis [${1}].</li></ul>   
  
<p>These associations highlight the complex interplay between NMOSD and other autoimmune conditions, necessitating comprehensive management strategies for affected individuals.</p>

**User Comment:**

This answer was not comprehensive and did not completely identify overlapping autoimmune disorders with NMOSD. Answer is very basic, and did not provide the epidemiology, prevalence, or incidence of coexisting disorders.

**Additional Context:**

When reworded to "Are there autoimmune conditions that often coexist with NMOSD?" we were provided a correct answer. This did not include prevalence but we did not ask for that specifically in the question. I do not believe there is a paper in the system that addresses this specific information.

**Answer 7 in new release:**

**Comorbidities Associated with NMOSD**

Neuromyelitis optica spectrum disorders (NMOSD) are rare, chronic, autoimmune, inflammatory disorders of the central nervous system (CNS) characterized by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis [[7A]](https://companion-dev.amgen.com/c/669634c25b5af9b3dc39010a). NMOSD is frequently associated with other antibody-mediated autoimmune disorders, which can significantly impact the clinical management and prognosis of affected individuals.

**Common Comorbidities**

**1. Myasthenia Gravis**

Myasthenia gravis (MG) is one of the most frequently coexisting conditions with NMOSD. It is an autoimmune disorder characterized by weakness and rapid fatigue of any of the muscles under voluntary control. The coexistence of MG with NMOSD is more frequent than expected, with NMOSD usually occurring several years after the diagnosis of myasthenia gravis [[1A]](https://companion-dev.amgen.com/c/669634c25b5af9b3dc39010a). This association highlights the need for clinicians to monitor NMOSD patients for symptoms of MG and vice versa.

**2. Systemic Lupus Erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is another autoimmune disorder commonly associated with NMOSD. SLE is characterized by the immune system attacking its own tissues, causing widespread inflammation and tissue damage in the affected organs. The presence of SLE in NMOSD patients suggests a shared underlying autoimmune mechanism [[1A]](https://companion-dev.amgen.com/c/669634c25b5af9b3dc39010a).

**3. Sjogren's Syndrome**

Sjogren's syndrome is an autoimmune disease that targets the glands that produce moisture, leading to dry mouth and dry eyes. It is also frequently associated with NMOSD. Like other autoimmune conditions, the coexistence of Sjogren's syndrome with NMOSD underscores the importance of comprehensive autoimmune screening in NMOSD patients [[1A]](https://companion-dev.amgen.com/c/669634c25b5af9b3dc39010a).

**Clinical Implications**

The association of NMOSD with these autoimmune disorders necessitates a multidisciplinary approach to patient care. The presence of comorbid autoimmune conditions can complicate the clinical picture and may require tailored therapeutic strategies to manage both NMOSD and the associated autoimmune disorder effectively.

**Conclusion**

NMOSD is frequently associated with other antibody-mediated autoimmune disorders, including myasthenia gravis, systemic lupus erythematosus, and Sjogren's syndrome. These associations highlight the complex autoimmune nature of NMOSD and the need for comprehensive management strategies to address the multifaceted clinical challenges presented by these comorbidities [[1A]](https://companion-dev.amgen.com/c/669634c25b5af9b3dc39010a).

**Details required:**

The response goes more into detail with respect to each of the identified medical conditions  
It provides prevelance and a short description against each condition  
  
If queried, as the next query ("could you provide the epidemiology, prevalence, incidence of coexisting disorder against each condition?"), a response is received with the mentioned points. Require feedback from med affairs team, if the points are relevant

**Question 8:** What is the long-term infection risk in patients on UPLIZNA?

**Response 8 (old release)**

<h2>Long-Term Infection Risk in Patients on UPLIZNA</h2>

<p>Long-term use of B cell depleting monoclonal antibodies like UPLIZNA is associated with reduced immunoglobulin levels, which can predispose patients to infections [${1}].</p>

<h3>Infection Rates and Common Infections</h3><ul> <li>The overall infection rate per 100 person-years during the N-MOmentum trial for any inebilizumab exposure was 23, with a decrease observed after more than 1 year on treatment [${1}].</li> <li>Common infections during the trial included urinary tract infection (UTI), nasopharyngitis, upper respiratory tract infection (URTI), and influenza, with most infections being mild to moderate in severity [${1}].</li></ul>

<h3>Immunoglobulin Levels and Infection Risk Monitoring</h3><ul> <li>B cell depleting therapies, including inebilizumab, can lead to a decline in total and individual immunoglobulin levels, such as IgG and IgM, with continued therapy [${5}].</li> <li>Patients on inebilizumab should have their Ig levels monitored at the beginning, during, and after discontinuation of therapy to assess for immune compromise and infection risk [${5}].</li></ul>

<p>Overall, while long-term use of UPLIZNA may reduce immunoglobulin levels and predispose patients to infections, monitoring Ig levels and promptly addressing any signs of immune compromise are essential to manage infection risks effectively [${1}][${5}].</p>

**User Comment:**

This response seems to somewhat answer the question, but tangentally goes into low immunoglobulins. The infections cited from N-MOmentum are correct, but this answer also appears to be missing data from the Cree end of study results.

**Additional Context:**

The answer was much more robust when replacing the word "risk" with rate"

**Answer 8 in new release:**

**Long-Term Infection Rates in Patients Treated with UPLIZNA**

UPLIZNA (inebilizumab-cdon) is a CD19-directed cytolytic antibody used for treating neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Understanding the long-term infection rates in patients treated with UPLIZNA is crucial for evaluating its safety profile.

**Clinical Trial Data**

**N-MOmentum Study**

The N-MOmentum study provides extensive data on the safety and tolerability of inebilizumab, including infection rates over both the randomized controlled period (RCP) and the open-label extension (OLE) phase.

* **Overall Infection Rate**: The overall infection rate per 100 person-years during the RCP and OLE phases for any inebilizumab exposure was 23 [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3). This rate decreased after more than one year of treatment and remained stable with continued exposure [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **Common Infections**: The most common infections observed were urinary tract infection (UTI), nasopharyngitis, upper respiratory tract infection (URTI), and influenza [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3). These infections were mostly mild to moderate in severity [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).

**Long-Term Safety and Tolerability**

**Infection Rates Over Time**

* **Stable Infection Rates**: A post hoc analysis evaluating the use of inebilizumab over four years found that infection rates did not increase over time [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3). This indicates a stable infection risk with prolonged treatment.
* **No New Safety Signals**: Long-term inebilizumab treatment was generally well tolerated, with no new safety signals identified [[1A][2A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3). This includes the absence of increased rates of infection or infusion-related reactions over time [[1A][2A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).

**Immunoglobulin Levels and Infection Risk**

**Hypogammaglobulinemia**

* **Reduced Immunoglobulin Levels**: Long-term use of B cell-depleting monoclonal antibodies like inebilizumab is associated with reduced immunoglobulin (Ig) levels, which can predispose patients to infections [[3A][4A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3). Monitoring Ig levels is recommended, especially in patients with opportunistic or recurrent infections [[3A][4A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **No Direct Association**: During the randomized controlled phase and the open-label extension, no direct association was found between low Ig levels and the occurrence of any infection or an infection greater than grade 3 [[4A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).

**Monitoring and Management**

**Infection Monitoring**

* **Pre-Infusion Screening**: Patients should be screened for active infections before each infusion of inebilizumab. Treatment should be delayed in patients with active infections until the infection is resolved [[6A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **Concomitant Medications**: The use of inebilizumab with other immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).

**Summary of Findings**

* **Infection Rate**: The overall infection rate for inebilizumab-treated patients was 23 per 100 person-years, with rates decreasing after one year and remaining stable with continued treatment [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **Common Infections**: UTIs, nasopharyngitis, URTIs, and influenza were the most common infections, generally mild to moderate in severity [[3A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **Long-Term Safety**: No increase in infection rates or new safety signals were observed with long-term inebilizumab treatment [[1A][2A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).
* **Immunoglobulin Levels**: Reduced Ig levels were noted, but no direct link to increased infection rates was established [[4A]](https://companion-dev.amgen.com/c/669a20965b5af9b3dc3903b3).

In conclusion, long-term treatment with UPLIZNA shows a stable infection rate with no significant increase over time, and the therapy is generally well tolerated. Regular monitoring of immunoglobulin levels and pre-infusion infection screening are recommended to manage infection risks effectively.

**Details required:**

Information needed regarding the data expected from Cree end of study results for further analysis  
Require context regarding the presence of low immunoglobins in the response