Kidney Outcomes in Patients With Active Lupus Nephritis Treated With Obinutuzumab:
A Post Hoc Analysis of the Phase 2 NOBILITY Trial

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B cells are central to the pathogenesis of systemic lupus erythematosus and lupus nephritis. Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody with enhanced B-cell killing vs other anti-CD20s due to:

- **Glycoengineering:**
  Up to 100x antibody-dependent cytotoxicity.

- **Type II binding conformation:**
  Greater direct cell death, reduced internalization and less reliance on complement-dependent cytotoxicity.

Obinutuzumab is currently not indicated for the treatment of lupus nephritis.

Nobility study design

104-week double-blind period

Obinutuzumab 1000 mg + SOC (n=63*)

Placebo + SOC (n=62)

**Key inclusion criteria:**
- ISN/RPS class III or IV (± V) LN by biopsy within 6 months
- UPCR >1 g/g on 24-hour collection

**Prespecified α level = 0.2**
SOC = MMF (or MPA) and CS

**Primary endpoint:** percentage of patients achieving CRR† (Week 52)

**Key secondary endpoints:** overall renal response (CRR† or PRR‡); change in levels of dsDNA, C3 and C4; improvement in UPCR and exploratory analyses at Weeks 76 and 104

**MMF (MPA):** target dose of 2.0-2.5 g/day of MMF (or equivalent)

**Corticosteroids:** 1-3 infusions of methylprednisolone 1000 mg IV prior to randomization and oral prednisone 0.5 mg/kg tapered to 7.5 mg/day by Week 12 and held

**Key exclusion criteria:** rapidly progressive glomerulonephritis; eGFR <30 mL/min/1.73 m²; >50% of glomeruli with sclerosis

CRR, complete renal response; CS, corticosteroids; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HPF, high-powered field; ISN, International Society of Nephrology; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OBI, obinutuzumab; PBO, placebo; PRR, partial renal response; R, randomization; RBC, red blood cell; RPS, Renal Pathology Society; SOC, standard of care; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

*One patient randomly assigned to obinutuzumab did not receive obinutuzumab due to pregnancy.
*†A composite measure requiring UPCR <0.5, normal renal function (serum creatinine ≤ ULN) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts).
‡A composite measure requiring ≥50% reduction in UPCR from baseline to a value <1 (to <3 if baseline UPCR was ≥3), serum creatinine not increased >15% from baseline and urinary sediment <10 RBCs/HPF or ≤50% increase over the baseline value.

CRR* was greater with obinutuzumab at all time points

CRR* in patients with lupus nephritis†

CRR, complete renal response.

* A composite measure requiring UPCR <0.5, normal renal function (serum creatinine ≤ ULN) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts).
† The Δ values may not exactly correspond to the subtraction of the patient percentages due to rounding.
‡ The prespecified α level was 0.2.

**Objective:** To evaluate kidney outcomes in patients with lupus nephritis treated with obinutuzumab in the Phase 2, randomized, double-blind, placebo-controlled NOBILITY trial (NCT02550652)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Methodology</th>
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<tbody>
<tr>
<td>Time to first unfavorable kidney outcome</td>
<td>Cox regression analysis</td>
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<tr>
<td>Treatment failure, doubling of serum creatinine or death</td>
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<tr>
<td>Chronic eGFR slope</td>
<td>Linear mixed-effects model</td>
</tr>
<tr>
<td>Assessed from Week 12 to 104*</td>
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</table>

eGFR, estimated glomerular filtration rate.

*eGFR slope was assessed from Week 12 to 104 to mitigate the influence of any acute changes that may have occurred in response to treatment (ie, exposure to high-dose glucocorticoids).
Post hoc study results
Obinutuzumab significantly reduced the risk of unfavorable kidney outcomes

HR, 0.40; 95% CI, 0.20 to 0.80

*Unfavorable kidney outcomes include treatment failure, doubling of serum creatinine and death. The total number of kidney outcomes (obinutuzumab vs placebo) were 12 vs 24 for treatment failure, 1 vs 6 for creatinine doubling and 1 vs 4 for death.
Summary of unfavorable kidney outcomes

Hazard ratio for unfavorable kidney outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Unfavorable kidney outcomes</td>
<td>0.40 (0.20 to 0.80)</td>
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</table>

Unfavorable kidney outcome, n

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Obinutuzumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Creatinine doubling</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>4</td>
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</tbody>
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HR, hazard ratio.
Obinutuzumab significantly attenuated eGFR slope decline compared with placebo.

**Population level–predicted eGFR**

**Table:**

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<tr>
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<th>Estimate</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>OBI slope</td>
<td>−0.43</td>
<td>−3.16 to 2.31</td>
</tr>
<tr>
<td>PBO slope</td>
<td>−4.52</td>
<td>−7.41 to −1.66</td>
</tr>
<tr>
<td>Slope difference of OBI from PBO</td>
<td>4.10</td>
<td>0.14 to 8.10</td>
</tr>
</tbody>
</table>

**Graph:**

- **eGFR, estimated glomerular filtration rate; OBI, obinutuzumab; PBO, placebo.**

Annual slope difference, 4.10 mL/min/1.73 m²/year; 95% CI, 0.14 to 8.08
Conclusions

Treatment with obinutuzumab:
- Increased CRR rates
- Decreased the risk of unfavorable kidney outcomes
- Reduced eGFR decline

These results suggest better long-term preservation of kidney function with obinutuzumab treatment.

Obinutuzumab is currently being evaluated in patients with active proliferative lupus nephritis in the global registrational Phase 3 REGENCY trial (NCT04221477).

CRR, complete renal response; eGFR, estimated glomerular filtration rate.