

RESULTS FROM THE REGENCY TRIAL ASSESSING EFFICACY AND SAFETY OF OBINUTUZUMAB IN ACTIVE LUPUS NEPHRITIS

Brad H. Rovin,¹ Richard A. Furie,² Jay P. Garg,³ Mittermayer B. Santiago,⁴ Gustavo Aroca-Martínez,⁵
Adolfina Elizabeth Zuta Santillán,⁶ Harini Raghu,³ Imran Hassan,⁷ Bongin Yoo,³ Elsa Martins,⁸ Himanshi Sehgal,⁸ Theodore A. Omachi,³ Thomas Schindler,⁸ William F. Pendergraft III,³ and Ana Malvar⁹ for the REGENCY Trial Investigators

¹Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH, USA; ²Division of Rheumatology, Northwell Health, Great Neck, NY, USA; ³Genentech, Inc., South San Francisco, CA, USA; ⁴Bahiana School of Medicine and Public Health and UFBA, Federal University of Bahia, and Clínica SER da Bahia, Salvador, Brazil; ⁵Universidad Simón Bolívar, Barranquilla, Colombia y Clínica de la Costa, Barranquilla, Colombia; ⁶Instituto de Ginecología y Reproducción, Lima, Peru; ⁷Hoffmann-La Roche Ltd, Mississauga, ON, Canada;

⁸F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁹Organización Médica de Investigación, Buenos Aires, Argentina

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Disclosures

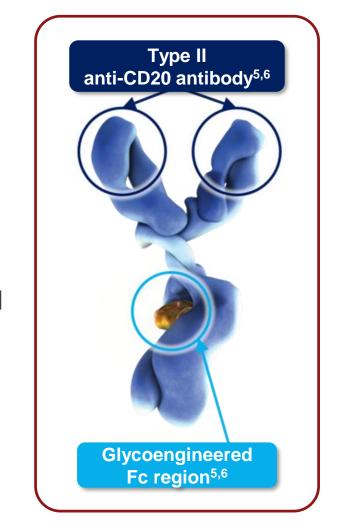
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- M.B. Santiago, G. Aroca-Martínez and A.E. Zuta Santillán have nothing to disclose.
- J.P. Garg, H. Raghu, B. Yoo, T.A. Omachi and W.F. Pendergraft III are employees of Genentech, Inc. and shareholders of F. Hoffmann-La Roche Ltd.
- I. Hassan and E. Martins are employees of F. Hoffmann-La Roche Ltd.
- H. Sehgal and T. Schindler are employees and shareholders of F. Hoffmann-La Roche Ltd.
- A. Malvar has received consulting fees from Genentech, Inc. and F. Hoffmann-La Roche Ltd.
- Obinutuzumab is not approved for the treatment of lupus nephritis

Lupus Nephritis: Unmet Medical Need and Involvement of B Cells

- Treatment of lupus nephritis remains sub-optimal, with morbidity and mortality significantly increased in individuals with SLE
 - The risk of ESKD from lupus nephritis remains high¹
- B cells are central to lupus nephritis pathogenesis, but no statistically significant improvement in outcomes has been shown when adding type I anti-CD20 antibodies to standard therapy^{2,3}
 - Variability in B-cell depletion may be responsible for inconsistent clinical responses³
 - There is no anti-CD20 therapy currently approved for lupus nephritis
- Obinutuzumab, a type II anti-CD20 antibody, provides enhanced B-cell depletion compared with type I antibodies, and could improve the treatment of lupus nephritis
- This was tested in the Phase II NOBILITY study,⁴ providing evidence for the efficacy and safety of obinutuzumab, which was further investigated in this Phase III REGENCY study

Obinutuzumab: A Type II Anti-CD20 Antibody

- Obinutuzumab is a humanized type II anti-CD20 approved for the treatment of CLL and follicular lymphoma^{1,2}
- Obinutuzumab resulted in enhanced B-cell depletion compared with rituximab or ofatumumab in oncology³⁻⁵:
 - Glycoengineering: Up to 100x greater antibody-dependent cellular cytotoxicity^{5,6}
 - Type II binding conformation: Greater direct cell death, reduced internalization, less reliance on complement-dependent cytotoxicity^{5,6}
- Enhanced peripheral and tissue B-cell depletion has been shown in animals and humans with obinutuzumab^{5,7}

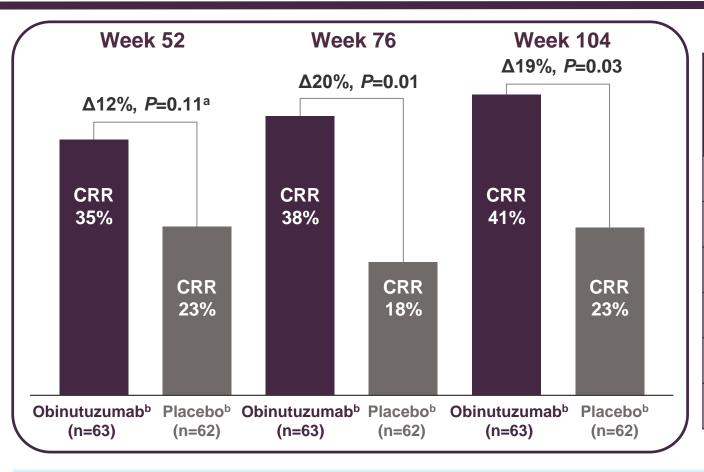


CLL, chronic lymphocytic leukemia.

^{1.} Davies A, et al. Future Oncol 2022;18:2943-2966; 2. Gazyva [prescribing information]. South San Francisco, CA: Genentech, Inc, 2022. (https://www.gene.com/download/pdf/gazyva_prescribing.pdf);

^{3.} Goede V. N Engl J Med. 2014;370:1101-1110. 4. Marcus R, et al. N Engl J Med. 2017;377:1331-1344. 5. Mössner E, et al. Blood 2010;115:4393-4402; 6. Herter S, et al. Mol Cancer Ther 2013;12:2031-2042;

Phase II NOBILITY Study (NCT02550652) Efficacy and Safety



Safety Event, Patients, n (%) (Up to Week 104)	Obinutuzumab Plus ST (n=64)	Placebo Plus ST (n=61)
Any AE	58 (91)	54 (89)
Deaths	1 (2)	4 (7)
Serious AE	16 (25)	18 (30)
Serious infection AE	5 (8)	11 (18)
Infection AE	48 (75)	38 (62)
IRR°	10 (16)	6 (10)

Primary endpoint of NOBILITY was met (improvement in CRR^a at Week 52); no new safety signals

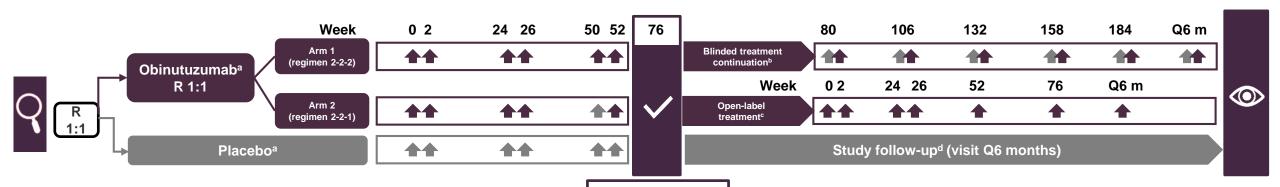
AE, adverse event; CRR, complete renal response; HPF, high-power field; IRR, infusion-related reaction; RBC, red blood cell; ST, standard therapy; UPCR, urine protein-to-creatinine ratio.

^a The primary endpoint was CRR at Week 52: a composite measure requiring UPCR <0.5, normal renal function (serum creatinine ≤ upper limit of normal) without worsening of baseline serum creatinine by >15% and inactive urinary sediment (<10 RBCs/HPF without RBC casts). Statistical significance was prespecified at an alpha of 0.2; ^b Plus ST of mycophenolate mofetil plus glucocorticoids; ^c Events that occurred in at least 5% of patients in the obinutuzumab plus ST group.

REGENCY Phase III Study Design



The REGENCY study evaluated the efficacy and safety of obinutuzumab compared with placebo in patients with active lupus nephritis when added to ST consisting of MMF plus glucocorticoids



Primary endpoint

- Q Screening
- ✓ Primary and secondary endpoints
- Study unblinding
- Obinutuzumab infusion 1000 mg
- Placebo infusion

Primary endpoint: CRR at Week 76 (UPCR <0.5 g/g, eGFR ≥85% of baseline, and no intercurrent events of rescue therapy, treatment failure, death, or early study withdrawal)

Secondary endpoints: Included CRR with prednisone ≤7.5 mg/day between Weeks 64 and 76, UPCR <0.8 g/g with no intercurrent events, change in eGFR from baseline to Week 76, and renal-related events or death through Week 76

Target MMF dose: 2.0-2.5 g/day

IV methylprednisolone: At least one dose (250–1000 mg) prior to first infusion

Prednisone dose: 0.5 mg/kg/day until Day 15 at which point tapered to 5 mg/day by Week 24 and maintained until Week 80

CRR, complete renal response; eGFR, estimated glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil; Q, quarter; R, randomized; ST, standard therapy; UPCR, urine protein-to-creatinine ratio.

^a Plus ST of MMF plus glucocorticoids; ^b Patients with an adequate treatment response at Week 76 continued to receive blinded infusions every 6 months starting at Week 80, until study unblinding; ^c Patients with inadequate treatment response at Week 76 or with loss of response during blinded treatment after Week 80 could enter open-label treatment; ^d Patients were followed through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo.

Study Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Adults 18-75 years
- Classification criteria for SLE according to ACR
- Active ISN/RPS class III or IV lupus nephritis with or without class V, on kidney biopsy performed ≤6 months before or during screening
- Positive anti-nuclear antibody (≥1:80 on Hep-2 cells or
 ≥1 equivalent anti-nuclear antibody test)
- ≥1 dose of pulse methylprednisolone IV (≥250 mg) or equivalent treatment for the current episode of active lupus nephritis from
 6 months prior to screening through Day 1 prior to the first infusion

Key Exclusion Criteria

- eGFR <30 mL/min/1.73m² of body surface area
- UPCR <1 g/g
- ESKD requiring dialysis or transplantation
- Active infection
- Anti-CD20 therapy <9 months before or during screening
- Cyclophosphamide, tacrolimus, cyclosporine or voclosporin
 ≤2 months before or during screening

Baseline Demographic and Clinical Characteristics

	Obinutuzumab Plus ST ^a (n=135)	Placebo Plus ST ^a (n=136)
Race (stratification factor) Black Other	15 (11.1%) 120 (88.9%)	17 (12.5%) 119 (87.5%)
Region (stratification factor) United States and Canada Latin America and the Caribbean Other	20 (14.8%) 77 (57.0%) 38 (28.1%)	20 (14.7%) 77 (56.6%) 39 (28.7%)
Age (year) Mean (SD) Median (min-max)	33 (10.5) 30 (18-64)	32.7 (10.0) 31 (18-72)
Sex (female)	114 (84.4%)	115 (84.6%)
Ethnicity (Hispanic or Latino)	71 (52.6%)	85 (62.5%)
eGFR (mL/min/1.73m²) Mean (SD) Median (min-max)	102.8 (29.3) 107 (15-164)	101.9 (32.2) 109 (13-166)
24-hour UPCR (g/g) Mean (SD) Median (min-max)	3.14 (2.99) 2.13 (0.2-21.6)	3.53 (2.76) 2.76 (0.1-13.3)

Treatment arms were generally well balanced

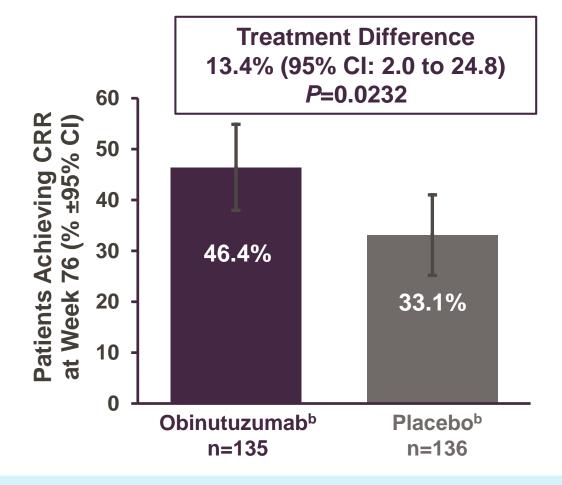
Primary Endpoint: CRR at Week 76



Primary Endpoint: CRR at Week 76

Includes all of the following:

- UPCR <0.5 g/g
- eGFR ≥85% of baseline
- No intercurrent events of rescue therapy, treatment failure^a, death and/or early study withdrawal

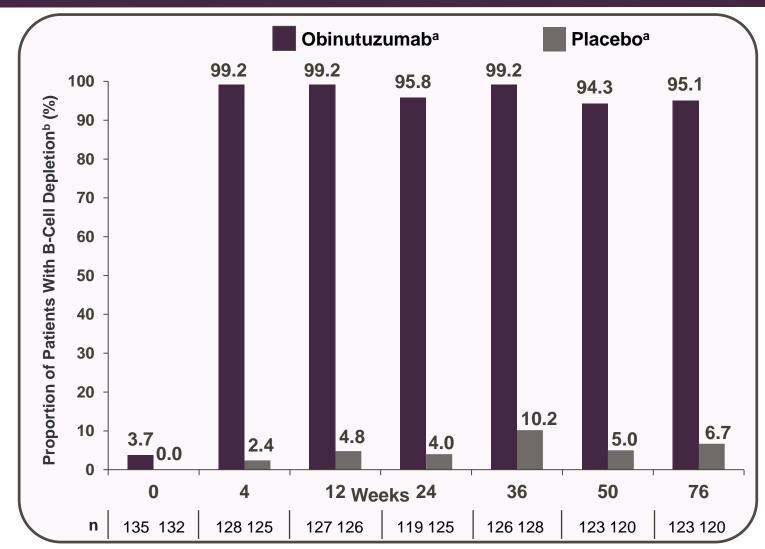


Primary endpoint of REGENCY was met

CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UPCR, urine protein-to-creatinine ratio.

^a Treatment failure definition (one or more): New ESKD or need for chronic dialysis or renal transplantation; clinically significant, sustained worsening of UPCR and/or eGFR from Week 24 onward that led the investigator to conclude the patient had failed the randomized treatment regimen; receipt of rescue therapy, except for glucocorticoid-only rescue; ^b Plus ST of mycophenolate mofetil plus glucocorticoids.

Proportion of Patients With B-Cell Depletion Over Time

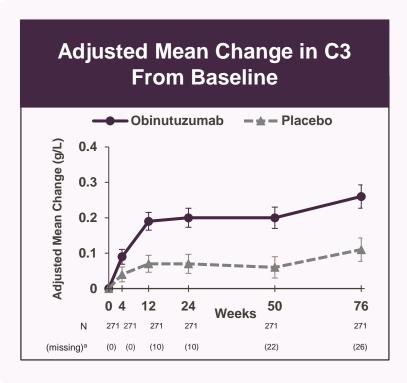


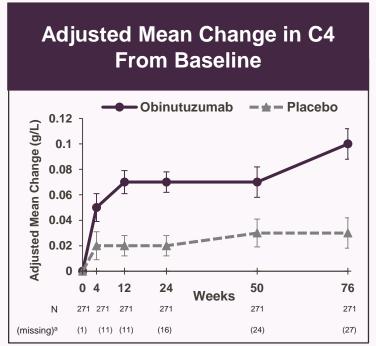
A higher proportion of patients in the obinutuzumab group achieved deep depletion of peripheral CD19+ B cells compared with the placebo group

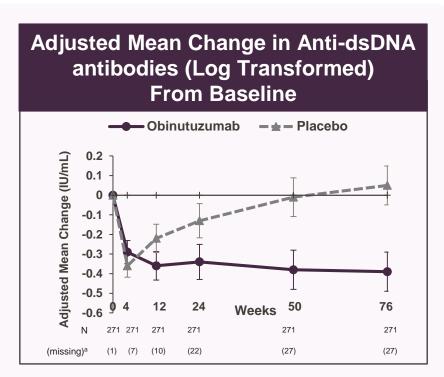
SE, standard error; ST, standard therapy

^a Plus ST of mycophenolate mofetil plus glucocorticoids. ^b B-cell depletion is defined as an absolute CD19-positive B-cell count <10 cells/µL.

Serologic Results







The obinutuzumab^b group showed greater adjusted mean changes in C3, C4 and anti-dsDNA antibody levels from baseline to Week 76 compared with the placebo^b group

Key Secondary Endpoints

Secondary Endpoints	Obinutuzumab Plus ST ^a (n=135)	Placebo Plus ST ^a (n=136)	Treatment Difference (95% CI)	<i>P</i> Value
CRR at Week 76 with prednisone taper (≤7.5 mg/day between Weeks 64 and 76), % (95% CI)	42.7 (34.32 to 51.09)	30.9 (23.12 to 38.65)	11.88 (0.57 to 23.18)	0.0421
Proteinuric response at Week 76 (UPCR <0.8 g/g and no intercurrent events ^b), % (95% CI)	55.5 (47.09 to 63.95)	41.9 (33.62 to 50.20)	13.68 (2.01 to 25.36)	0.0227
Mean change in eGFR (kidney function) from baseline to Week 76, adjusted mean, mL/min/1.73m ² (SE)	2.31 (2.713)	-1.54 (2.706)	3.84 (-1.83 to 9.51)	0.1842
Death or renal-related events ^c through to Week 76, % (95% CI)	18.9 (12.11 to 25.61)	35.6 (27.50 to 43.78)	-16.83 (-27.42 to -6.23)	0.0026 ^d
ORR (PRRe or CRR) at Week 50, % (95% CI)	59.1 (50.80 to 67.43)	50.7 (42.16 to 59.22)	8.36 (-3.41 to 20.12)	0.1670
Change in FACIT-Ff from baseline to Week 76, adjusted mean, points (SE)	1.76 (1.223)	3.11 (1.212)	-1.35 (-3.89 to 1.20)	0.2991

More patients achieved CRR with lower prednisone^g and a proteinuric response with obinutuzumab Death and renal-related events were nominally significant but statistical significance cannot be claimed^d

CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; ORR, overall renal response; PRR, partial renal response; SE, standard error; ST, standard therapy; UPCR, urine protein-to-creatinine ratio.

^a ST of mycophenolate mofetil plus glucocorticoids; ^b Intercurrent events were receipt of rescue therapy, treatment failure, death and/or early study withdrawal; ^c One or more of death, treatment failure, worsening proteinuria (confirmed ≥50% increase in UPCR ≥3) and worsening eGFR (confirmed ≥30% decrease in eGFR to <60); ^d Statistical significance cannot be claimed as endpoints earlier in the hierarchy were not met; ^e ≥50% reduction in UPCR from baseline, UPCR <1 g/g (or <3 g/g if the baseline UPCR was ≥3 g/g), eGFR ≥85% of baseline AND no intercurrent events^c; ^f A 13-item scale with scores ranging from 0 to 52, with higher scores indicating less fatigue; ^g Prednisone dose of 7.5 mg per day or lower between Weeks 64 and 76.

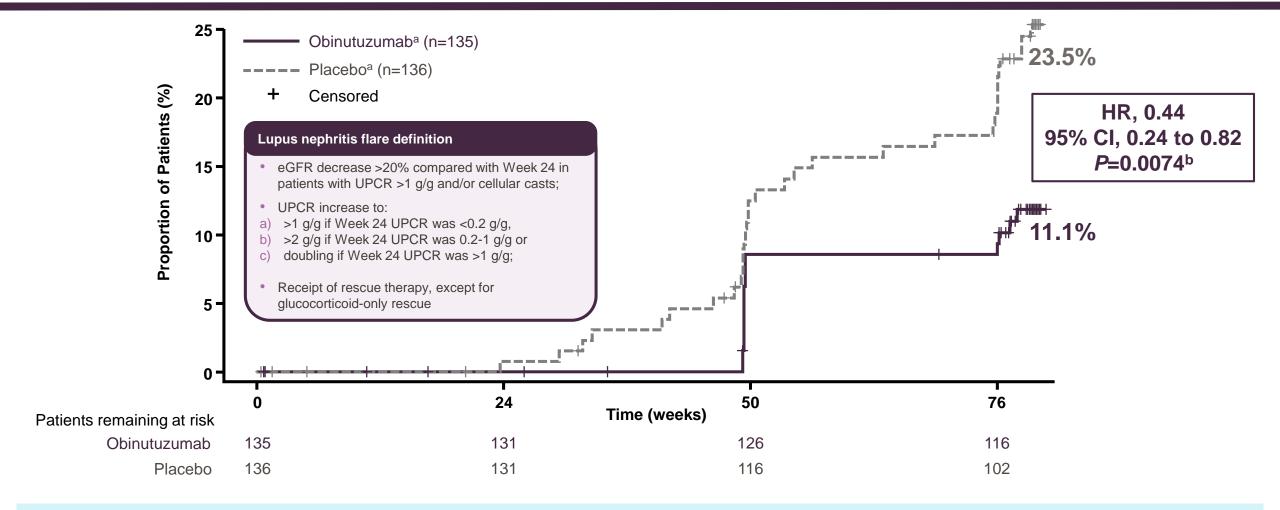
Intercurrent Events at Week 76 in ITT Population

Patients, n (%)	Obinutuzumab Plus ST ^a (n=136)	Placebo Plus ST ^a (n=132)
≥1 intercurrent event	15 (11.1)	34 (25.0)
Treatment failure	5 (3.7)	24 (17.6)
Chronic dialysis	0	1 (0.7)
Clinically significant, sustained worsening in UPCR and/or eGFR from Week 24	5 (3.7)	22 (16.2)
ESKD	0	2 (1.5)
Rescue therapy excluding glucocorticoid-only rescue	4 (3.0)	20 (14.7)
Rescue therapy	8 (5.9)	24 (17.6)
Corticosteroid-only rescue therapy	5 (3.7)	11 (8.1)
Death	3 (2.2)	1 (0.7)
Early study withdrawal	9 (6.7)	13 (9.6)
AE	0	1 (0.7)
Death	3 (2.2)	1 (0.7)
Lost to follow-up	0	1 (0.7)
Other	0	2 (1.5)
Physician decision	0	3 (2.2)
Withdrawal by patient	6 (4.4)	5 (3.7)

A numerically higher number of intercurrent events was observed in the placebo group

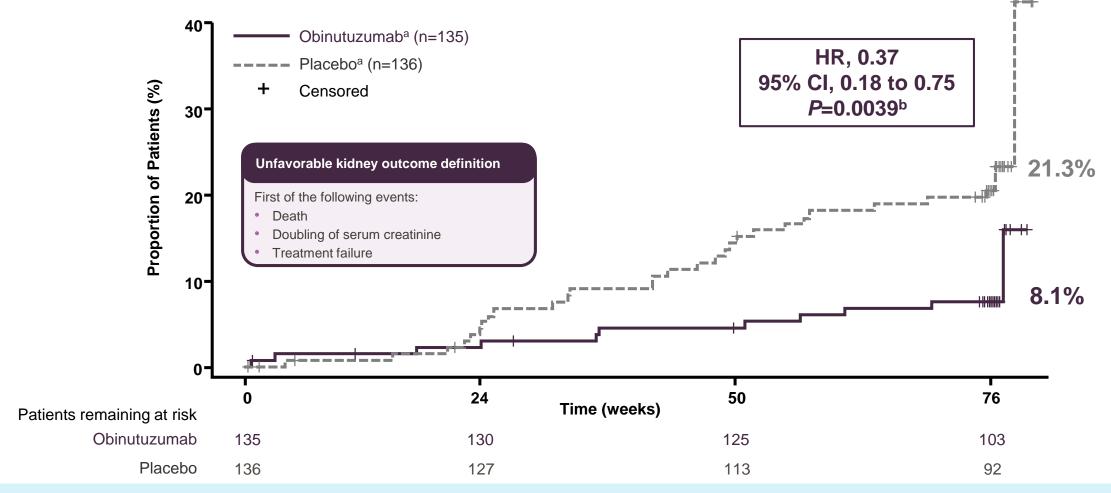
^a ST of mycophenolate mofetil plus glucocorticoids.

Exploratory Analysis: Time to Lupus Nephritis Flare From Weeks 24 Through 76



Obinutuzumaba treatment reduced the risk of lupus nephritis flare by 56%

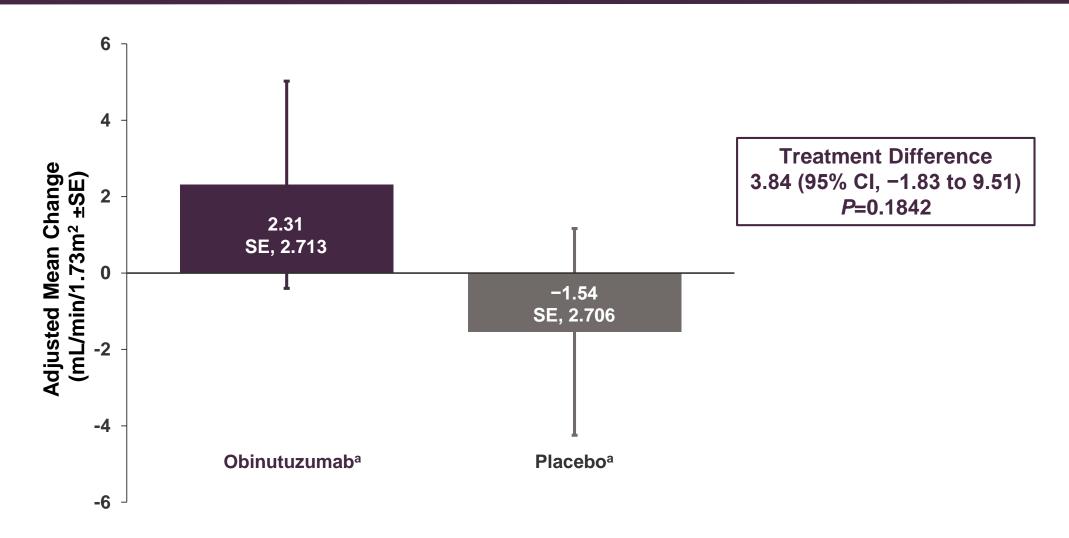
Exploratory Analysis: Time to an Unfavorable Kidney Outcome Through Week 76



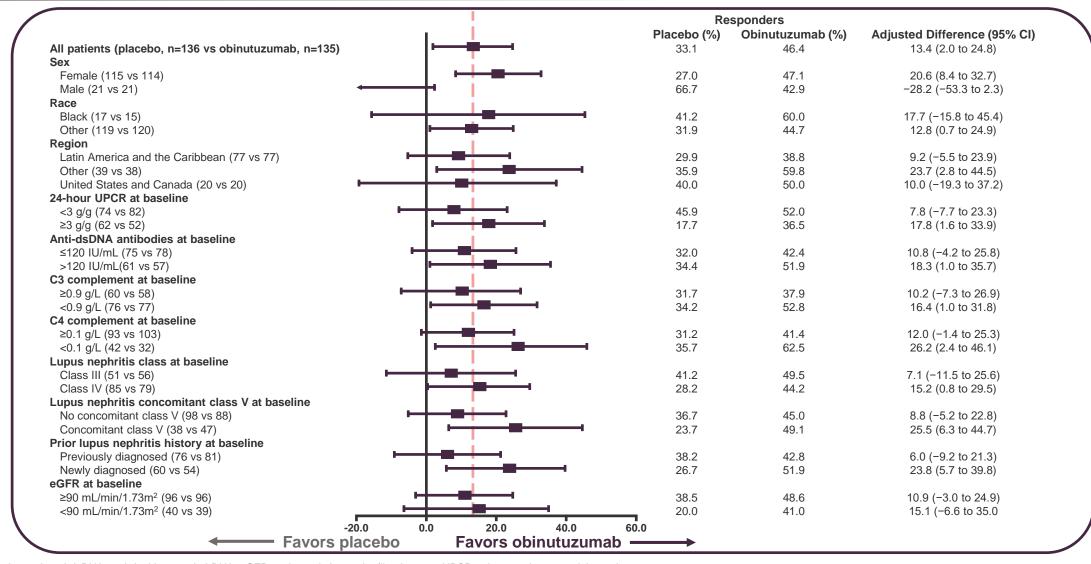
Obinutuzumab treatment reduced the risk of unfavorable kidney outcomes by 63%

Change in eGFR From Baseline to Week 76





Prespecified Subgroup Analyses of CRR at Week 76



Safety Summary: AEs

- Number of patients with ≥1 AE was comparable between arms
- Number of patients with serious AEs was numerically higher in obinutuzumab arm
 - Largely driven by serious infections, which were mainly related to COVID-19
 - With COVID-19 events excluded, serious infections decreased from 16.9% to 11.0% in the obinutuzumab arm, with no change in the placebo arm (7.6%)
 - Most serious AEs resolved or improved and did not lead to treatment discontinuation

Patients, n (%)	Obinutuzumab Plus ST ^a (n=136)	Placebo Plus ST ^a (n=132)	Total (N=268)
Patients with ≥1 AE [Total events]	126 (92.6) [748]	117 (88.6) [665]	243 (90.7) [1413]
Patients with ≥1 serious AE [Total events]	44 (32.4) [68]	24 (18.2) [35]	68 (25.4) [103]
AE leading to study discontinuation	0	0	0
Deaths	3 (2.2)	1 (0.8)	4 (1.5)
Serious AEs occurring in ≥5 total patients			
COVID-19 pneumonia	7 (5.1)	0	7 (2.6)
Pneumonia	4 (2.9)	3 (2.3)	7 (2.6)
Urinary tract infection	4 (2.9)	2 (1.5)	6 (2.2)
COVID-19	4 (2.9)	1 (0.8)	5 (1.9)
Gastroenteritis	3 (2.2)	2 (1.5)	5 (1.9)
Acute kidney injury	3 (2.2)	2 (1.5)	5 (1.9)

Safety Summary: AEs of Special Interest

Patients, n (%)	Obinutuzumab Plus ST ^a (n=136)	Placebo Plus ST ^a (n=132)	Total (N=268)
IRRs ^b	21 (15.4)	15 (11.4)	36 (13.4)
Grade 3-5 infection	21 (15.4)	9 (6.8)	30 (11.2)
Treatment-related neutropenia	17 (12.5)	5 (3.8)	22 (8.2)
Worsening of pre-existing cardiac conditions	0	2 (1.5)	2 (0.7)
Treatment-related thrombocytopenia	1 (0.7)	0	1 (0.4)
Any hepatitis B reactivation or progressive multifocal leukoencephalopathy	0	0	0
Gastrointestinal perforations	0	0	0
Met Hy's law criteria	0	0	0
Suspected transmission of an infectious agent by the study drug	0	0	0

AE, adverse event; IRR, infusion-related reaction; ST, standard therapy.

^a ST of mycophenolate mofetil plus glucocorticoids; ^b IRRs were defined as any AE occurring during or within 24 hours of IV infusion of obinutuzumab or placebo and judged by study investigators to be related to the infusion.

Safety Summary: Treatment-Related Neutropenia

Patients, n (%)	Obinutuzumab Plus ST ^a (n=136)	Placebo Plus ST ^a (n=132)	Total (N=268)
≥1 treatment-related AE, patients, n (%) [total events]	17 (12.5) [24]	5 (3.8) [7]	22 (8.2) [31]
Neutropenia	15 (11.0)	4 (3.0)	19 (7.1)
Leukopenia	2 (1.5)	0	2 (0.7)
Febrile neutropenia	1 (0.7)	0	1 (0.4)
Neutrophil count decreased	1 (0.7)	1 (0.8)	2 (0.7)

- All neutropenic events resolved except one, which has improved
- Blinded obinutuzumab dose was:
 - Not changed in 13 patients
 - Discontinued in 3 patients: 2 with serious neutropenia and 1 with serious febrile neutropenia
 - Reported as unknown in 1 patient

Conclusions

- REGENCY met its primary endpoint of CRR at Week 76
- Statistically significant and clinically meaningful differences were observed in:
 - CRR with prednisone ≤7.5 mg/day between Weeks 64 and 76
 - Proteinuric response (UPCR <0.8 g/g and no intercurrent events)
- No unexpected safety signals were identified
 - The number of patients with AEs were comparable between arms
 - More serious AEs occurred in the obinutuzumab^a arm, mainly infections and COVID-19-related events
 - The safety profile of obinutuzumab aligned with the well-characterized safety profile from hemato-oncology indications

First positive registrational study of a B-cell-depleting, anti-CD20 monoclonal antibody in patients with active lupus nephritis

REGENCY New England Journal of Medicine Publication



ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

Richard A. Furie, M.D., ¹ Brad H. Rovin, M.D., ² Jay P. Garg, M.D., ³ Mittermayer B. Santiago, M.D., ^{4,5,6} Gustavo Aroca-Martínez, M.D., ^{7,8} Adolfina Elizabeth Zuta Santillán, M.D., ⁹ Damaris Alvarez, M.D., ¹¹ Cleyber Navarro Sandoval, M.D., ¹⁰ Alexander M. Lila, M.D., ¹³ James A. Tumlin, M.D., ¹⁴ Amit Saxena, M.D., ¹⁵ Fedra Irazoque-Palazuelos, M.D., ¹⁶ Harini Raghu, Ph.D., ³ Bongin Yoo, Ph.D., ³ Imran Hassan, M.Sc., ¹⁷ Elsa Martins, Pharm.D., Ph.D., ¹⁸ Himanshi Sehgal, M.Sc., ¹⁸ Petra Kirchner, M.Sc., ¹⁸ Jorge Ross Terres, M.D., ³ Theodore A. Omachi, M.D., ³ Thomas Schindler, Ph.D., ¹⁸ William F. Pendergraft, III, M.D., Ph.D., ³ and Ana Malvar, M.D., ¹² for the REGENCY Trial Investigators*





THANK YOU FOR LISTENING