

A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PARTICIPANTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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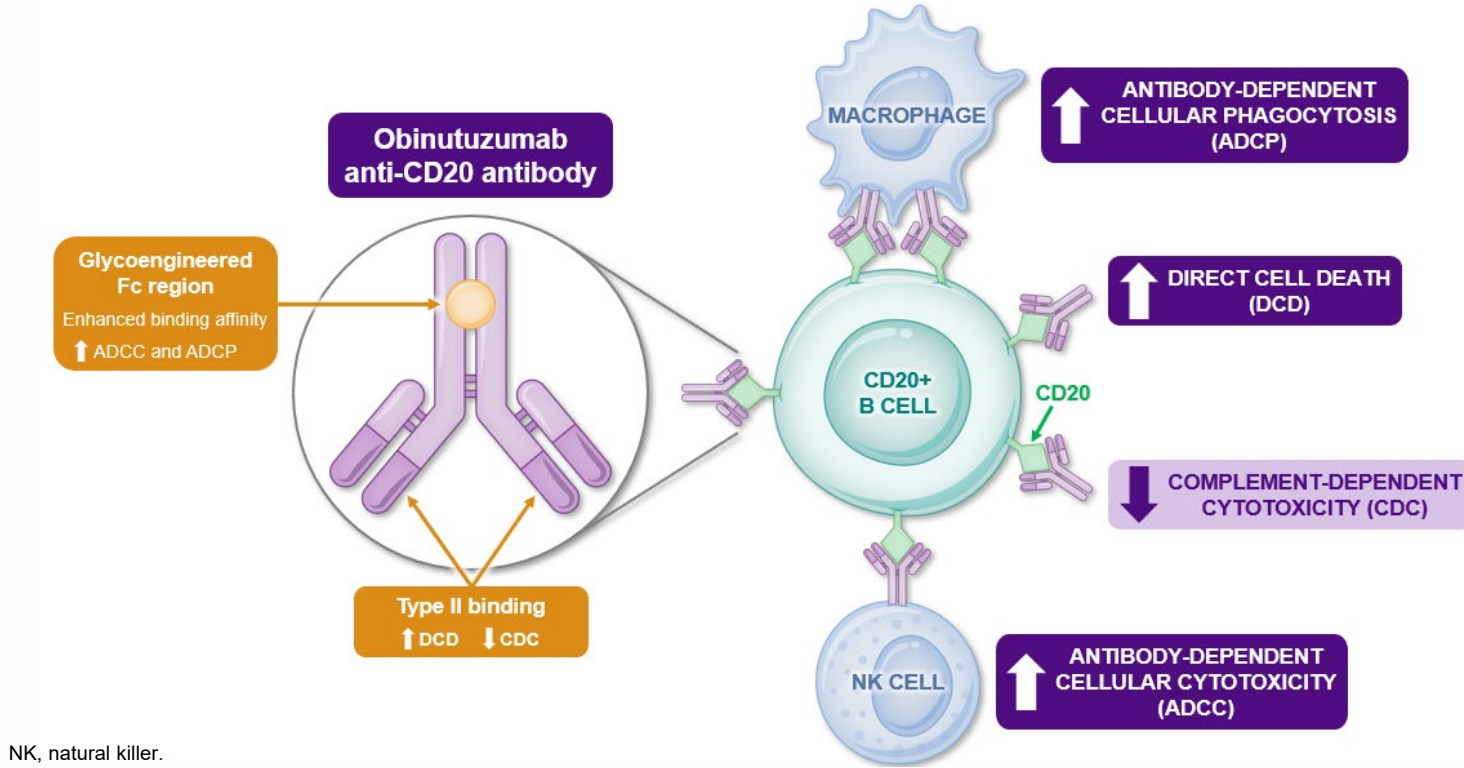
BACKGROUND

- Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that causes immune-mediated damage to multiple organs and affects more than 3.4 million people globally, with women of childbearing age most commonly affected¹
- Abnormalities in B cells caused by breaches in central and peripheral tolerance play a pivotal role in the pathogenesis of SLE^{2,3}
- Obinutuzumab is a recombinant, humanized, glycoengineered type II anti-CD20 IgG1 monoclonal antibody that leads to greater B-cell depletion compared with type I anti-CD20 antibodies; obinutuzumab leads to greater B-cell depletion compared with type I anti-CD20 antibodies through antibody-dependent cellular phagocytosis (ADCC), antibody-dependent cellular cytotoxicity (ADCP) and direct cell death (DCD) with less reliance on complement versus type I anti-CD20 antibodies⁴⁻⁶
- The efficacy and safety of obinutuzumab in lupus nephritis have now been confirmed in the Phase II NOBILITY (NCT02550652) and the Phase III REGENCY (NCT04221477) trials.^{7,8} In the REGENCY trial, the primary endpoint of complete renal response at Week 76 was achieved by 46.4% of participants treated with obinutuzumab plus standard therapy compared with 33.1% of participants treated with placebo plus standard therapy (adjusted difference 13.4%; 95% CI, 2.0 to 24.8; $P=0.02$)⁸

OBJECTIVES

- The Phase III ALLEGORY study (NCT04963296) aims to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of obinutuzumab compared with placebo in participants with SLE when added to standard therapy

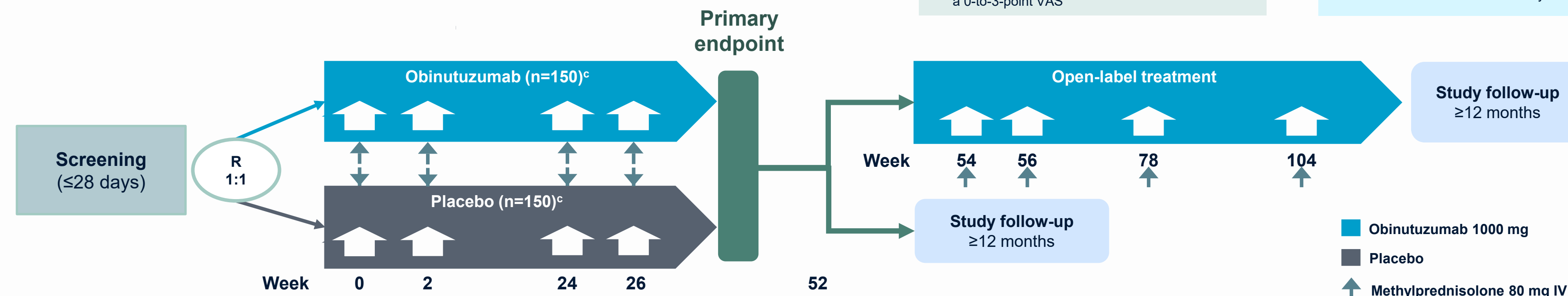
Obinutuzumab Mechanism of Action



ALLEGORY STUDY DESIGN AND STUDY POPULATION

Figure 1. ALLEGORY Study Design

- ALLEGORY is a parallel-group, double-blind, randomized, placebo-controlled study
- Participants with SLE with high disease activity^a and receiving at least one standard therapy^b for SLE were randomized 1:1 to receive blinded infusions of obinutuzumab (1000 mg) or placebo on Day 1 (Week 0) and at Weeks 2, 24 and 26
- After completing blinded treatment at Week 52, participants from both groups may enter an 18-month open-label treatment phase in which obinutuzumab is administered at Weeks 54, 56, 78 and 104
- Participants will be followed for at least 12 months from their last infusion to monitor safety and disease activity, with no further obinutuzumab infusions



SCREENING

- ≥1 standard SLE therapy at a stable dose:
 - Prednisone ≤30 mg/day (or equivalent)
 - One antimalarial
 - One immunosuppressant

WEEK 0 to WEEK 52

- Continuation of standard SLE therapies
- Prednisone taper to ≤5 mg/day by Week 24
- No change to prednisone dose after Week 40

Key Inclusion and Exclusion Criteria

- ✓ Aged 18-75 years
- ✓ Diagnosis of SLE^d ≥12 weeks prior to screening
- ✓ Taking at least one of: oral glucocorticoids, antimalarials, conventional immunosuppressants
- ✓ High disease activity^a at screening and Day 1: Modified SLEDAI-2K (EDAA) score ≥8, ≥1 BILAG A or ≥2 BILAG B (screening only), PGA score ≥1.0 on a 0-to-3-point VAS
- ✓ At least one of: ANA ≥1:80, anti-dsDNA, anti-Smith antibodies above ULN^e
- ✓ Low C3, C4 and/or CH50 complement levels^g
- ✗ No evidence of active infection
- ✗ No significant lupus-associated renal disease and/or impairment (e.g., UPCR >3.5 g/g) or active severe central nervous system SLE

Primary Endpoint

Proportion of participants who achieve SRI-4 response at Week 52, defined as all of the following:

- Reduction of at least 4 points in SLEDAI-2K from baseline
- No new BILAG category A or no more than one new BILAG category B item
- No worsening (increase) of ≥0.3 points on a 3-point PGA-VAS

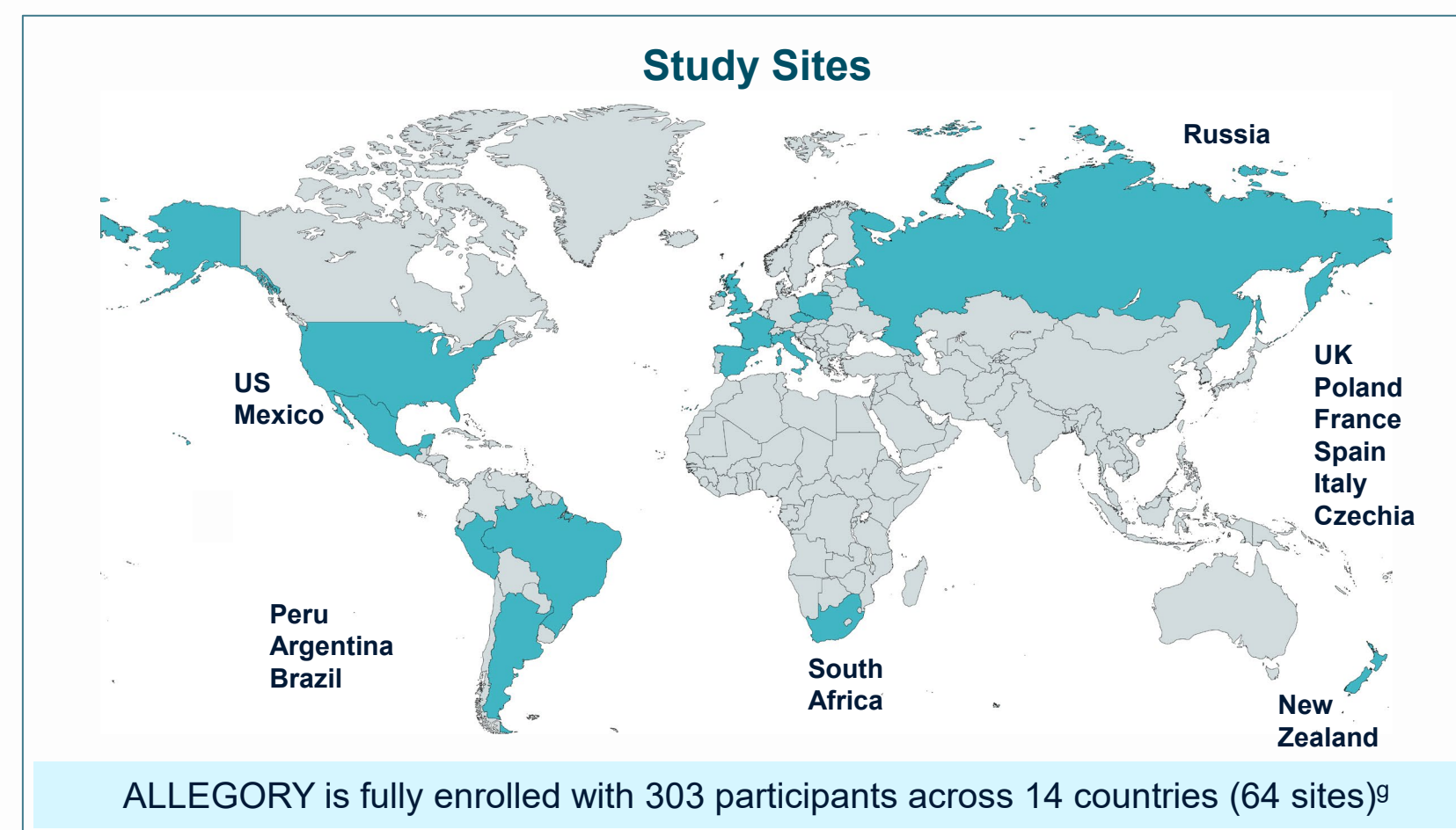
Key Secondary Endpoints

Proportion of participants who achieve the following:

- Achievement of or SRI-6^f at Week 52
- Time to first BILAG flare over 52 weeks
- Sustained glucocorticoid control from Weeks 40 to 52
- Sustained SRI-4 response from Weeks 40 to 52
- Achievement of BICLA response at Week 52
- Other Secondary Endpoints include:
 - Safety
 - PK profile of obinutuzumab

OPEN-LABEL TREATMENT

SLE therapies managed at investigator's discretion



^aHigh disease activity is defined as a modified SLEDAI-2K (EDAA) score ≥8, excluding points for alopecia, headache and fever; ≥1 BILAG A or ≥2 BILAG B and a PGA score ≥1.0; ^bStandard therapy of mycophenolate mofetil plus oral glucocorticoids, antimalarials or conventional immunosuppressants; ^cPlanned enrollment; ^dAccording to the 2019 EULAR/ACR Classification Criteria; ^eDetermined by the central laboratory at screening; ^fSRI-6 defined as reduction of at least 6 points in SLEDAI-2K from baseline, no new BILAG category A or no more than one new BILAG category B item, no worsening (increase) of 0.3 points or more on a 3-point PGA-VAS scale; ⁹Data as of November 2, 2024.

CONCLUSIONS

- Building on positive results observed in lupus nephritis trials, the ALLEGORY study will evaluate the efficacy and safety of obinutuzumab in participants with active SLE
- The ALLEGORY study is fully enrolled. Full results will be available upon study completion

Table 1. Demographic Characteristics of Participants in ALLEGORY

Characteristic	All Participants (N=303) ^a
Age (years)	
Mean (SD)	41.2 (12.4)
Median (min-max)	41.0 (18-70)
Male / Female, n (%)	29 (9.6) / 274 (90.4)
Race, n (%)	
American Indian or Alaska Native	86 (28.4)
Asian	6 (2.0)
Black or African American	47 (15.5)
Native Hawaiian or other Pacific Islander	1 (0.3)
White	125 (41.3)
Multiple	18 (5.9)
Unknown	20 (6.6)
Region, n (%)	
Africa	27 (8.9)
Asia-Pacific	2 (0.7)
Eastern Europe	45 (14.9)
Latin America	164 (54.1)
North America	37 (12.2)
Western Europe	28 (9.2)

^aData as of November 2, 2024.

- The median age of participants was 41.0 years
- The majority (90.4%) were female
- Participants were distributed across Latin America (54.1%), Eastern Europe (14.9%), North America (12.2%), Western Europe (9.2%), Africa (8.9%) and Asia-Pacific (0.7%)

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ABBREVIATIONS

ACR, American College of Rheumatology; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ANA, anti-nuclear antibodies; BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CDC, complement-dependent cytotoxicity; DCD, direct cell death; dsDNA, double-stranded DNA; EDAA, Eligibility Disease Activity Assessment; EULAR, European Alliance of Associations for Rheumatology; IV, intravenous; NK, natural killer; PGA, Physician's Global Assessment; PK, pharmacokinetics; R, randomized; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI, Systemic Lupus Erythematosus Responder Index; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio; VAS, visual analog scale.

DISCLOSURES

E.M.V. has received consulting fees from AbbVie, AstraZeneca, Eli Lilly and Company, F. Hoffmann-La Roche Ltd/Genentech, Inc., Merck, Novartis, Otsuka, Pfizer and UCB. Z.A. has received research support and/or provided advisory services for Amgen, AstraZeneca, GSK, Novartis, F. Hoffmann-La Roche Ltd and Kezar. S.P., S.K., G.R., A.E., Z.S. and B.W. have nothing to disclose. V.A.D. has received speaker and consulting fees from AbbVie, Novartis, Eli Lilly and Company, Johnson & Johnson, UCB, GSK, and AstraZeneca. M.A.D.A. has received speaker's fees from AbbVie, Amgen, BMS, Alfasigma, Johnson & Johnson, Eli Lilly, Novartis, UCB, J&J, and AstraZeneca; has received consulting fees from AbbVie, Johnson & Johnson, Novartis, MSD, Eli Lilly, BMS, and Cullinan; and has received grants from Pfizer, Abbvie, Novartis, UCB, Alfasigma, and AstraZeneca. F.I.P. has received consulting fees and/or research support from AbbVie, Amgen, Eli Lilly, F. Hoffmann-La Roche Ltd, Janssen, Novartis and Takeda. J.M. and J.P.G. are employees of Genentech, Inc. and shareholders of F. Hoffmann-La Roche Ltd. O.M. is an employee and shareholder of F. Hoffmann-La Roche Ltd. R.A.F. has received research support and consulting fees from Chugai Pharmaceutical Co., Ltd., F. Hoffmann-La Roche Ltd, Genentech, Inc. and GlaxoSmithKline; is a consultant for AstraZeneca, EMD Serono, Novartis, Biogen, and BMS; is an investigator for AstraZeneca, Novartis, Biogen, BMS, and Kyverna, and is a speaker for AstraZeneca.

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