Obexelimab, a B-cell inhibitor, in IgG4-Related Disease: Results from the Phase 3 INDIGO Trial

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Disclosures

Obexelimab is an investigational medicine and has not been approved by any regulatory authority for the treatment of IgG4-related disease.

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Background and need for novel treatment strategies

- **IgG4-related disease is a chronic relapsing** systemic disease
- **Glucocorticoids** (GCs) are effective but associated with **cumulative toxicity**
- **B-cell depletion** works but comes with relevant **limitations**

Background and need for novel treatment strategies

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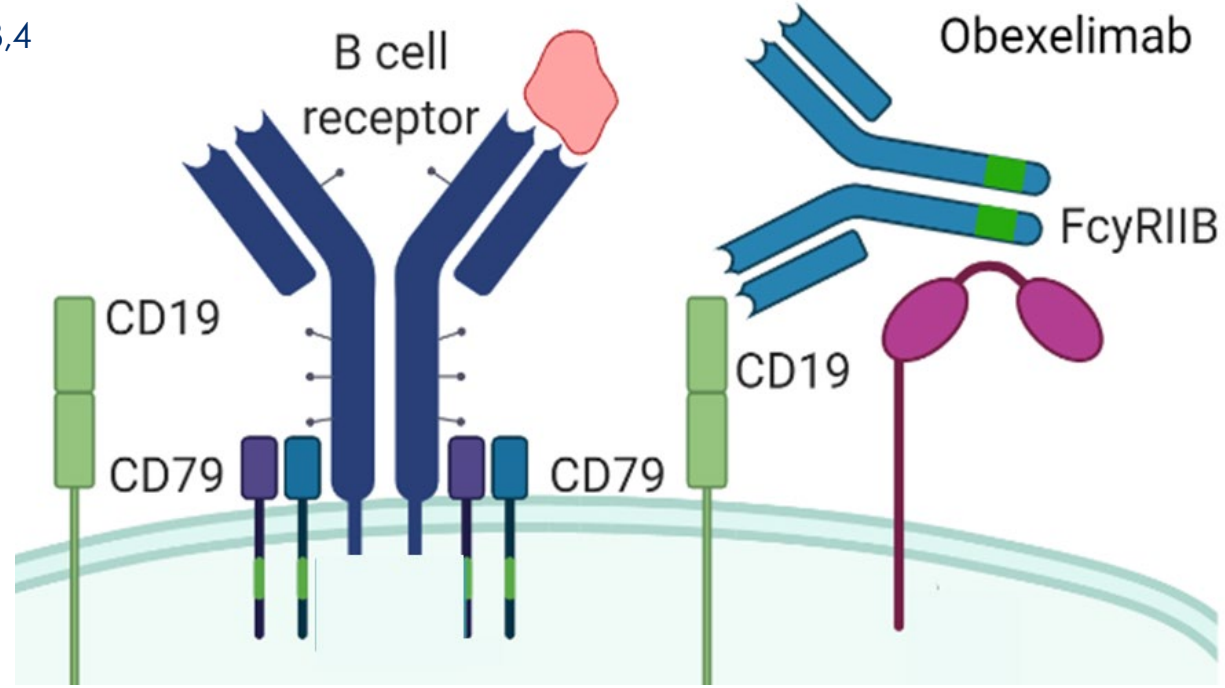
- **Glucocorticoids** (GCs) are effective but associated with **cumulative toxicity**
- **B-cell depletion** works but comes with relevant **limitations**

    1. **Prolonged immunosuppression**
    2. **Hypogammaglobulinemia**
    3. **Increased risk of infections**
    4. **Impaired vaccine response**
    5. **Intravenous administration**

Obexelimab and B-cell inhibition

- **Humanized** bifunctional monoclonal antibody
- Co-engagement of **CD19 and FcγRIIb**[1,2]
- **B-cell inhibition** with no antibody or complement dependent cytotoxicity[3,4]
- **Reversible partial B-cell reduction**[3,4]



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The INDIGO trial

- **Double-blind, randomized, placebo-controlled** trial (NCT05662241)
- To evaluate the **efficacy and safety of obexelimab, administered subcutaneously, in maintaining IgG4-related disease remission**

The INDIGO trial – Study Design

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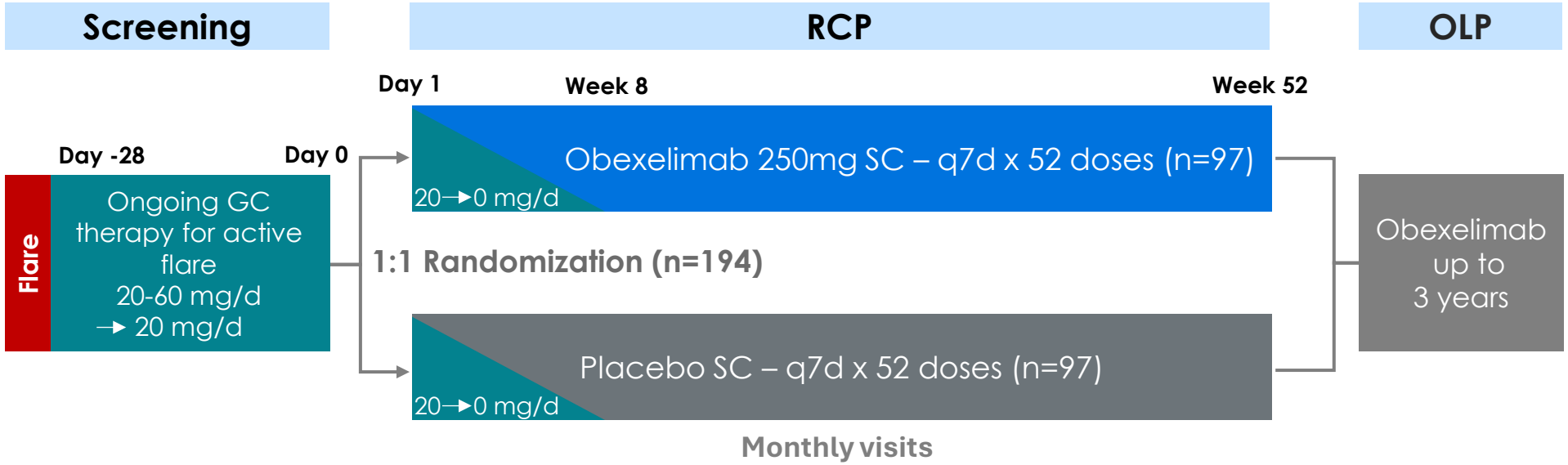
Inclusion
- Adults with IgG4-RD (ACR/EULAR-confirmed)
- Active disease **requiring** GC initiation/escalation

Exclusion
- Active infection
- Recent biologics or B-cell depletion
- High-dose steroids (>60 mg/day)



GC = glucocorticoids; q7d = every 7 days; SC = subcutaneous; RCP = Randomized Controlled Period; OLP = Open-Label Period.

Endpoints

Primary Endpoint

Time to first IgG4-RD flare requiring initiation of rescue therapy, in the opinion of the investigator and confirmed by the AC.

IgG4-RD = IgG4-related disease; AC = adjudication committee.

Endpoints

Key Secondary Endpoints

1. **Time to first investigator-determined flare** requiring initiation of rescue therapy

2. **Number of investigator- and AC-determined flares** requiring initiation of rescue therapy

3. Proportion of patients achieving **complete remission** at Week 52
   - No AC-determined flare
   - No treatment for flare
   - IgG4-RD RI = 0 or PGA VAS = 0 mm

4. **Cumulative dose of GC rescue therapy** through Week 52

IgG4-RD = IgG4-related disease; AC = adjudication committee; GC = glucocorticoid; RI = Responder Index; PGA VAS = Physician Global Assessment Visual Analog Scale.

Flare assessment and adjudication

- **Organ-specific flare criteria** developed by an international expert panel
- Flare criteria included detection of **subclinical/asymptomatic disease activity**
- **Imaging** at Week 52
- Flare determinations underwent blinded independent adjudication, with **majority-vote confirmation** of protocol-defined flares and need for rescue therapy

The largest clinical trial in IgG4-RD

- 194 patients enrolled from 15 countries across 114 sites: the largest clinical trial in IgG4-RD conducted to date reflecting the full disease spectrum

15 Countries

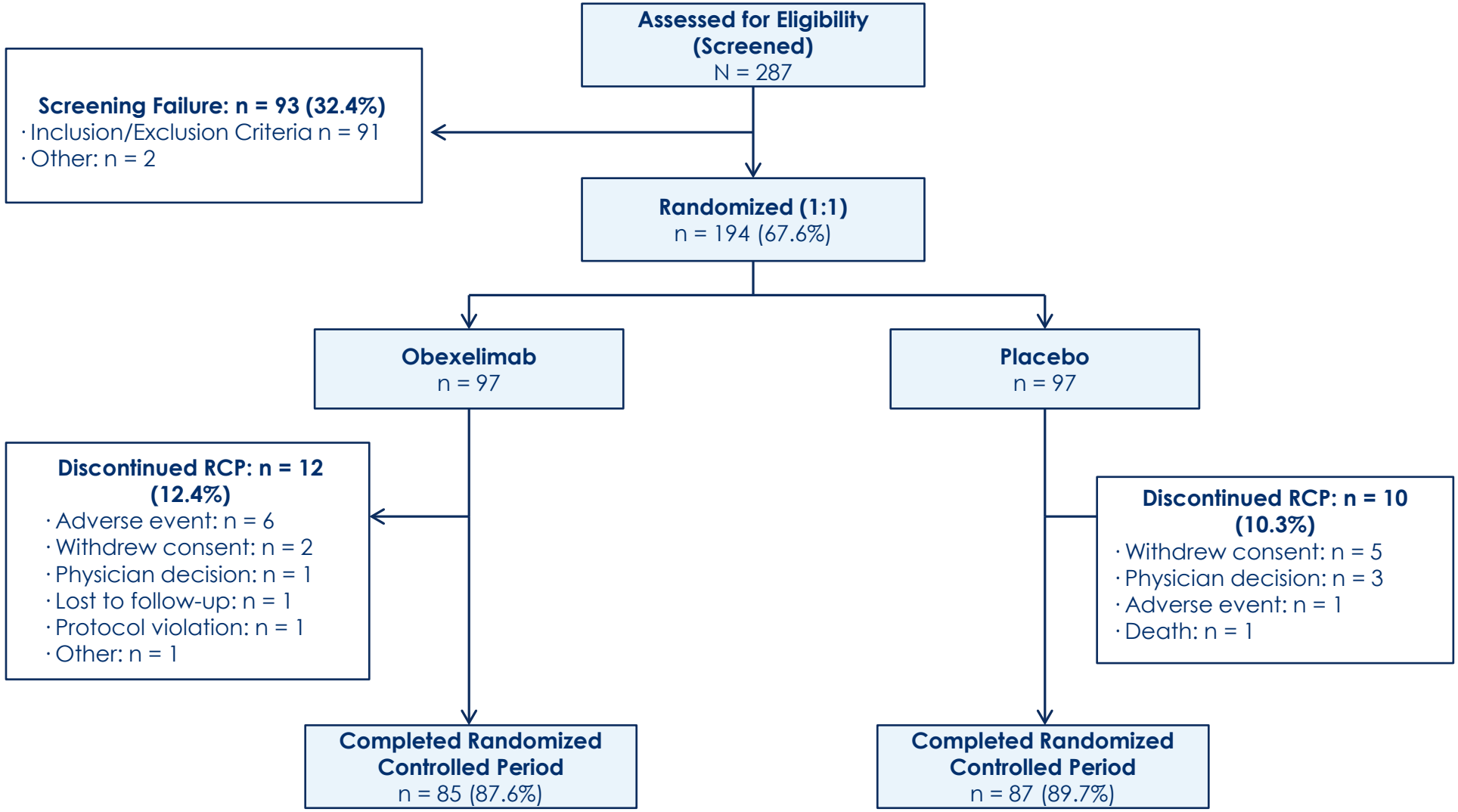
EAST ASIA
- China
- Japan
- Rep. of Korea
- Taiwan

EUROPE
- France
- Germany
- Italy
- Poland
- Spain
- Turkey
- United Kingdom

N. AMERICA
- Canada
- United States

LATIN AMERICA
- Argentina
- Mexico

Trial disposition



Baseline demographics

Characteristic	Obexelimab (N=97)	Placebo (N=97)
Age — yr	59.6 ± 13.4	58.7 ± 12.0
Male sex, n (%)	65 (67.0)	64 (66.0)
Race, n (%)		
Asian	59 (60.8)	51 (52.6)
White	27 (27.8)	39 (40.2)
Other	11 (11.3)	7 (7.2)
Region, n (%)		
Asia	51 (52.6)	48 (49.5)
US/Canada	24 (24.7)	16 (16.5)
Europe	19 (19.6)	28 (28.9)
Latin America	3 (3.1)	5 (5.2)

Clinical characteristics

Characteristic	Obexelimab (N=97)	Placebo (N=97)
IgG4-related disease manifestation		
Recurrent — no. (%)	64 (66.0)	65 (67.0)
Newly diagnosed — no. (%)	33 (34.0)	32 (33.0)
Number of organs involved — no. (%)		
1	6 (6.2)	7 (7.2)
2–4	59 (60.8)	58 (59.8)
>4	32 (33.0)	32 (33.0)
Most commonly affected organs — no. (%)		
Salivary gland	60 (61.9)	66 (68.0)
Lacrimal gland	54 (55.7)	49 (50.5)
Pancreas	45 (46.4)	46 (47.4)
Lymph nodes	41 (42.3)	46 (47.4)
Disease duration at screening* — yr	3.1 ± 4.2	2.5 ± 3.2
Median ACR–EULAR score (IQR)	38.0 (30.0–45.0)	38.0 (31.0–44.0)
Prior rituximab use — no. (%)	12 (12.4)	11 (11.3)

*Disease duration is defined as the time between the date of diagnosis of IgG4-RD (as reported by the investigator) and the screening visit.
IQR = interquartile range (25th–75th percentile).

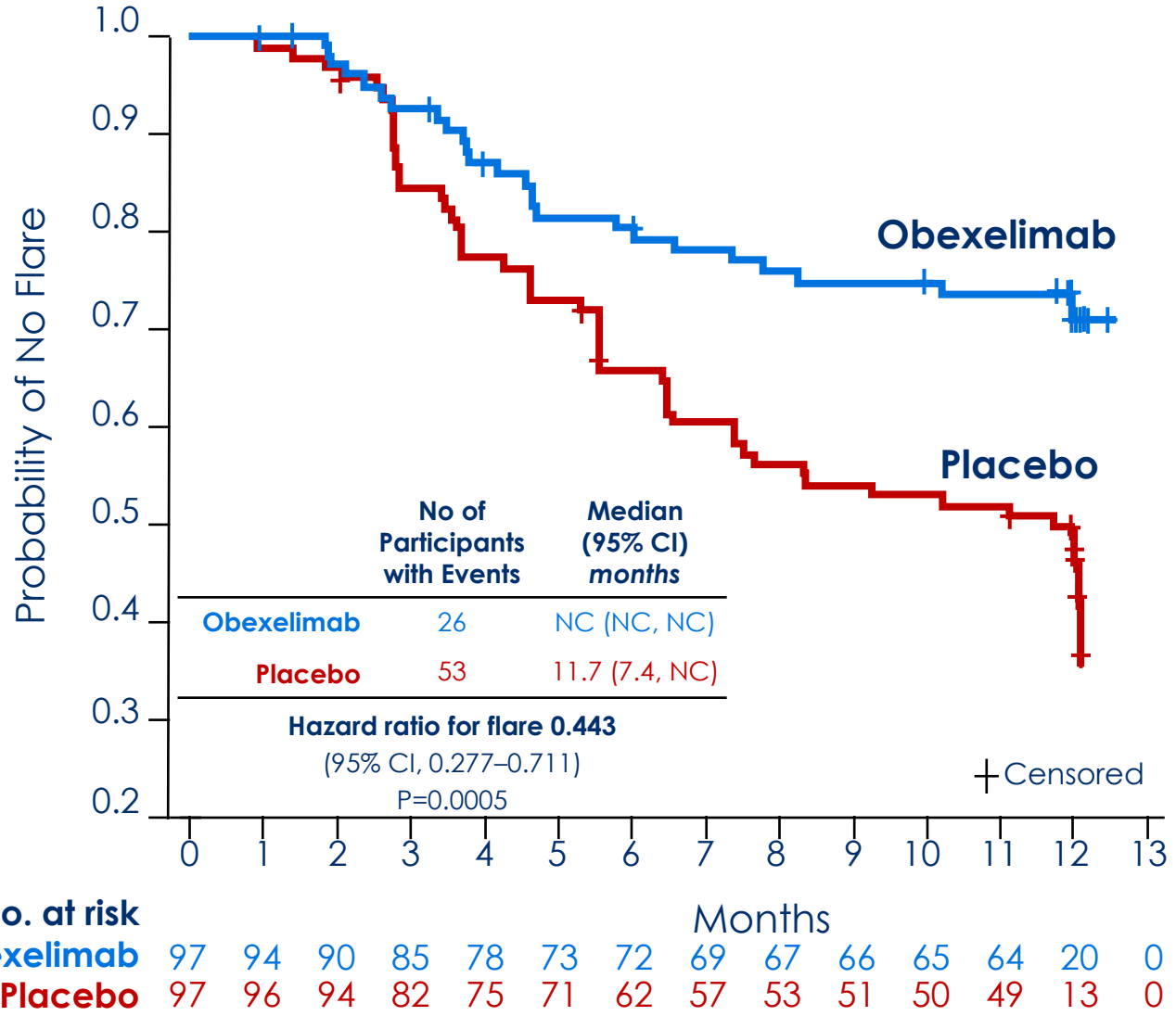
Results

Results – Obexelimab reduced the risk of IgG4-RD flares

PRIMARY ENDPOINT

73.2% of patients receiving obexelimab remained flare-free through Week 52

- Flares occurred in 26/97 patients receiving obexelimab (26.8%) and 53/97 receiving placebo (54.6%)
- **Hazard ratio, 0.443**; 95% CI, 0.277 to 0.711; P= 0.0005



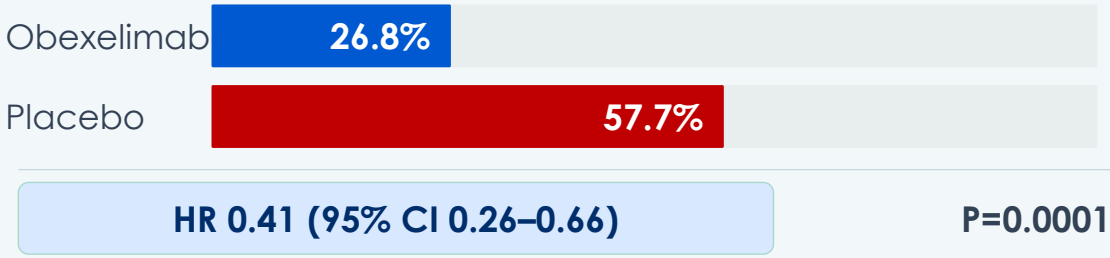
NC = Not Calculable.

Results – Obexelimab met all Key Secondary Endpoints

SECONDARY ENDPOINTS

Obexelimab Placebo

Time to first investigator-determined flare (Patients with ≥1 flare)

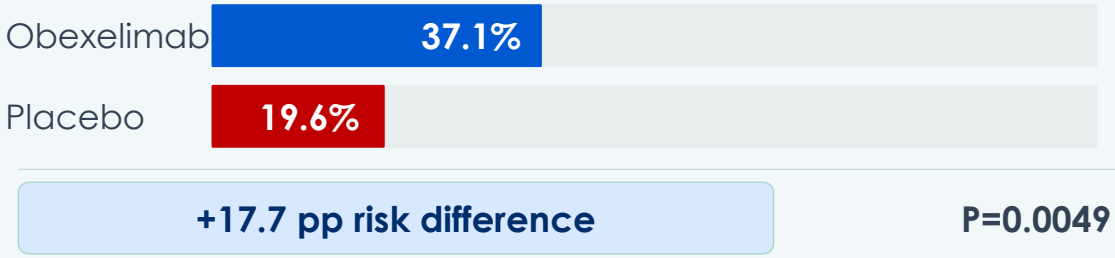


HR 0.41 (95% CI 0.26–0.66) P=0.0001

Annualized rate of adjudicated flares requiring rescue therapy (Flares/yr)

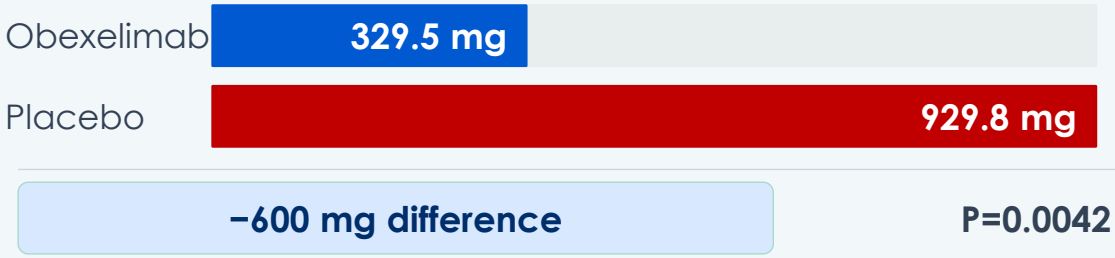
Rate ratio 0.48 (95% CI 0.32–0.74) P=0.0008

Patients achieving complete remission at Week 52



+17.7 pp risk difference P=0.0049

Cumulative glucocorticoid rescue dose through Week 52*



−600 mg difference P=0.0042

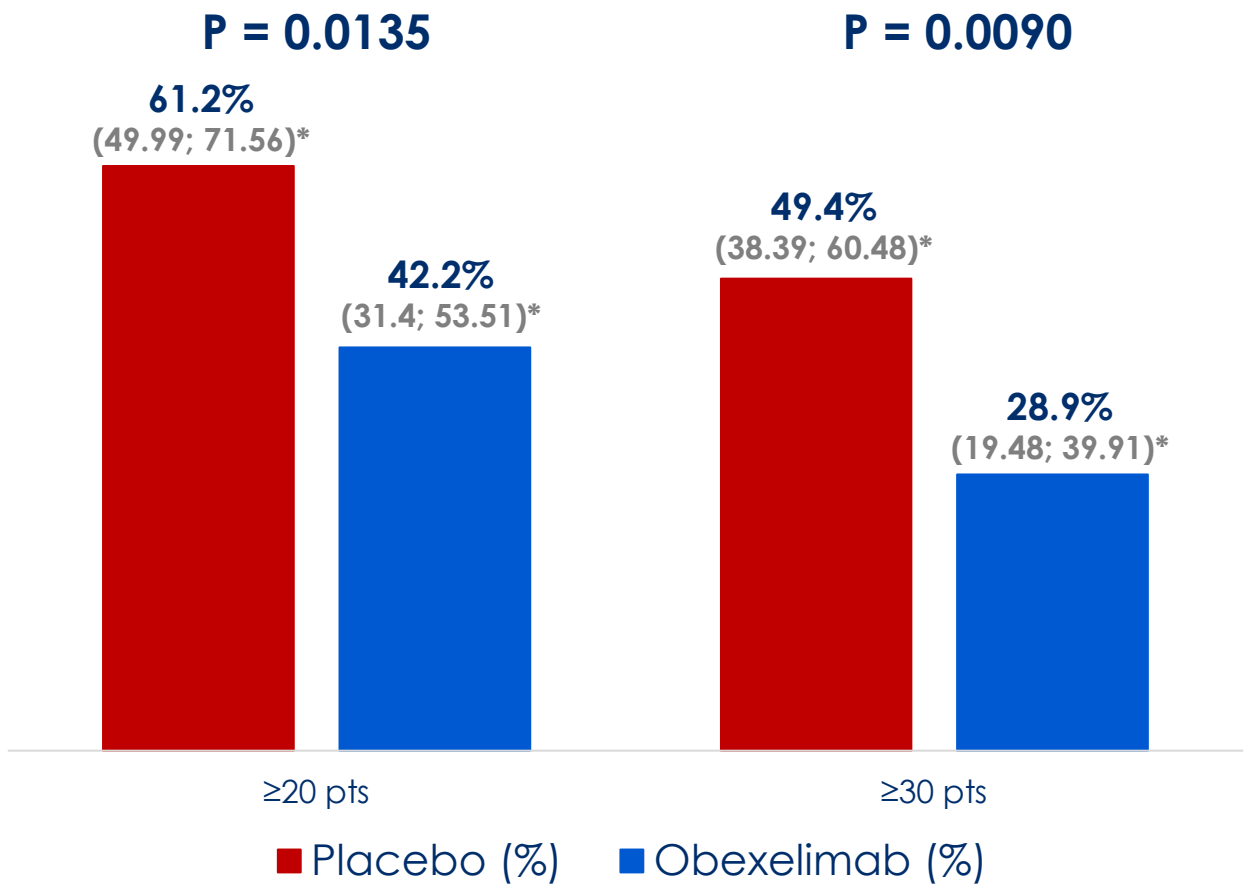
HR = hazard ratio; CI = confidence interval; pp = percentage points.
* GC exposure shown reflects rescue treatment for flare management; obexelimab was not administered with routine GC prophylaxis for hypersensitivity.

Results – Glucocorticoid Toxicity Index

Glucocorticoid Toxicity Index - Cumulative Worsening Score*

- GTI-CWS assesses accumulated glucocorticoid-related toxicity over time.
- Obexelimab was associated with less accumulated glucocorticoid toxicity at Week 52.

Proportion of Patients With ≥20- or ≥30-Point GTI-CWS at Week 52

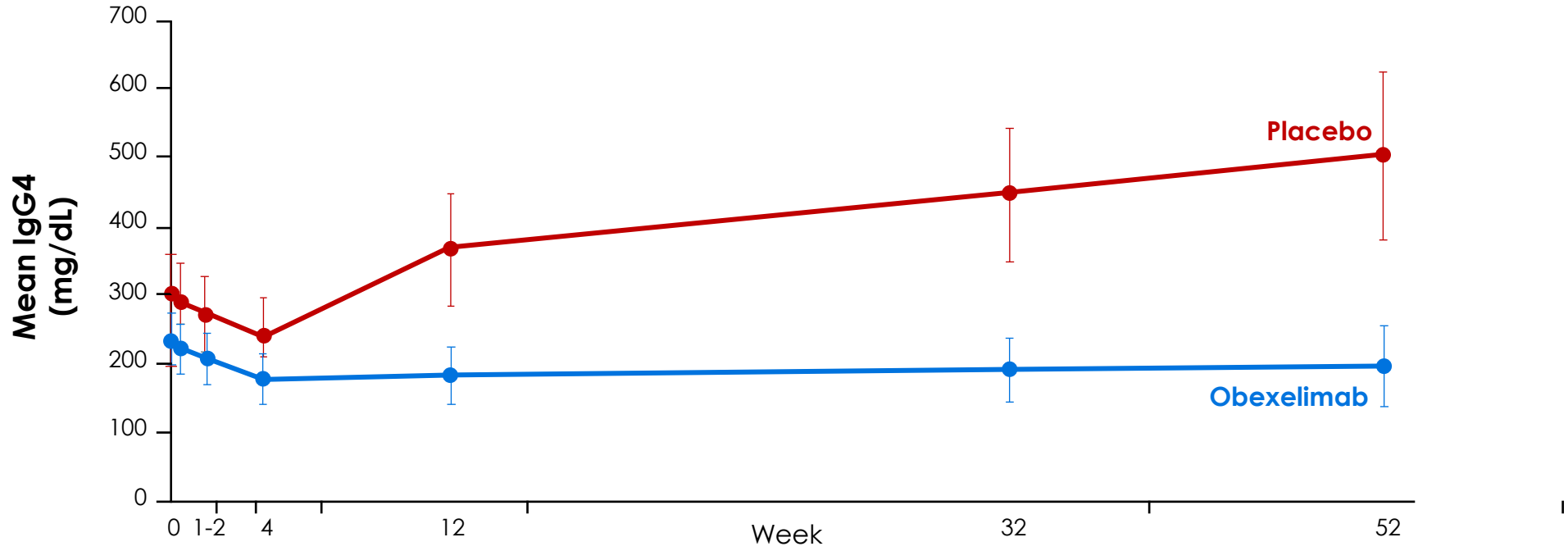


* 95% CI

*GTI domains assessed included body mass index, glucose tolerance, blood pressure, lipid metabolism, infection, glucocorticoid myopathy, skin toxicity, and neuropsychiatric effects; bone mineral density was not assessed.

Results – Sustained effect of Obexelimab on Serum IgG4

Serum IgG4 levels decline after GC induction was sustained through Week 52 with obexelimab but increase above baseline with placebo

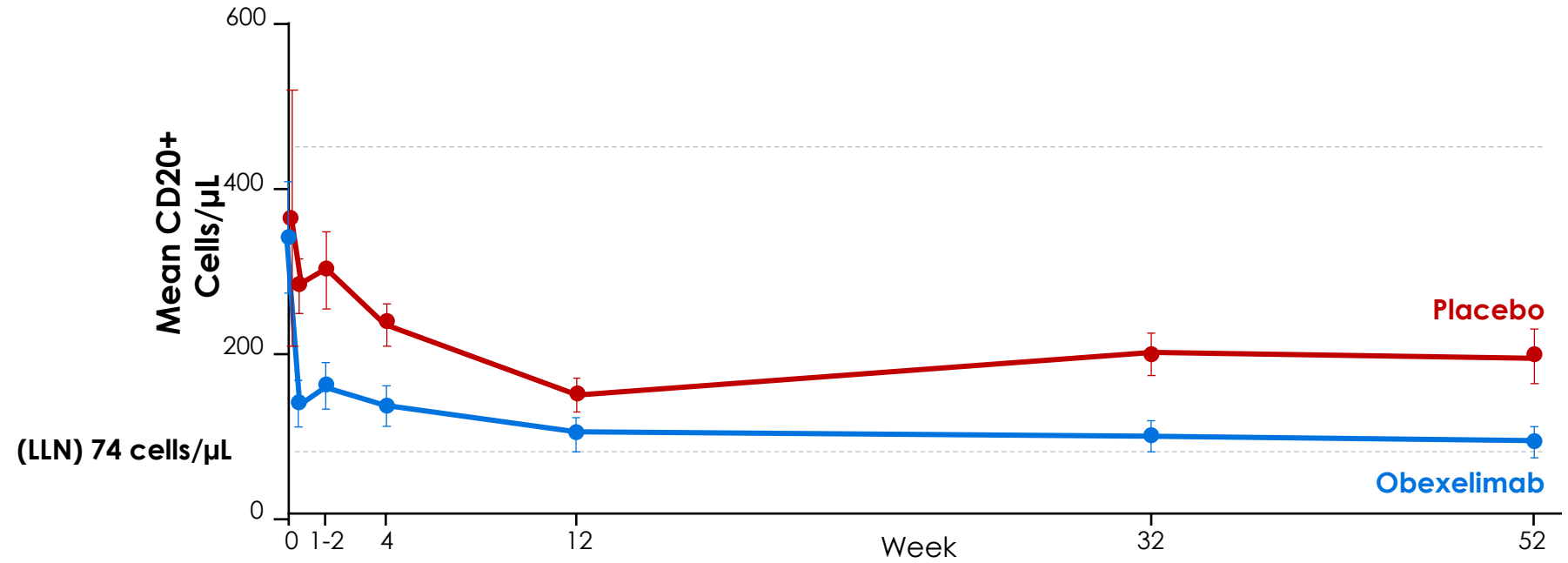


No of participants					
Obexelimab	91 87	86	79	67	60
Placebo	96 94	92	94	67	56

I bars indicate 95% confidence intervals.

Results – B cells remained above LLN through Week 52

Mean CD20+ B-cell counts decline after GC induction was sustained through Week 52 and remained above the LLN during obexelimab treatment



No of participants						
Obexelimab	97	96	94	84	72	63
Placebo	97	94	96	94	73	61

LLN = Lower Limit of Normal; I bars indicate 95% confidence intervals.

Results – Adverse Events

	Obexelimab (N=97)	Placebo (N=97)
Patients with ≥1 AE	95 (97.9%)	93 (95.9%)
Patients with ≥1 SAE	10 (10.3%)	18 (18.6%)
Patients with ≥1 Grade ≥3 AE	11 (11.3%)	23 (23.7%)
Patients with AE leading to discontinuation of treatment	9 (9.3%)	3 (3.1%)
Selected Treatment-emergent AEs (≥10 in either)		
Arthralgia	19 (19.6%)	11 (11.3%)
Nasopharyngitis	18 (18.6%)	14 (14.4%)
Upper respiratory infection	15 (15.6%)	22 (22.7%)
Insomnia	13 (13.4%)	10 (10.3%)
Back pain	11 (11.3%)	12 (12.4%)
Diarrhea	11 (11.3%)	6 (6.2%)
Adverse events of Special Interest		
Hypersensitivity (≥Grade 2)	16 (16.5%)	11 (11.3%)
Infections (≥Grade 3)	2 (2.1%)	4 (4.1%)
Malignancy*	3 (3.1%)	0
Injection site reaction (≥Grade 2)	2 (2.1%)	1 (1.0%)

* Three malignancies identified, all deemed unrelated: One renal cell carcinoma determined to be pre-existing before enrollment; One prostate cancer, for which there is no known increased risk with immunosuppression; One squamous cell carcinoma.

Conclusions

1. Obexelimab significantly **reduced the risk of IgG4-RD flare requiring rescue therapy** versus placebo through Week 52.
2. Obexelimab **reduced cumulative glucocorticoid rescue use** and was associated with less glucocorticoid toxicity worsening versus placebo.
3. Obexelimab was **generally well tolerated**, with no new safety signals identified.

Conclusions

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2. Obexelimab **reduced cumulative glucocorticoid rescue use** and was associated with less glucocorticoid toxicity worsening versus placebo.
3. Obexelimab was **generally well tolerated**, with no new safety signals identified.
4. INDIGO demonstrated that B-cell inhibition through CD19/FcγRIIb co-engagement may present a **novel treatment approach** for IgG4-RD.
5. INDIGO supports obexelimab as **a differentiated subcutaneous therapeutic approach** for IgG4-RD.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Obexelimab for the Treatment of IgG4-Related Disease

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