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A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Patients With IgAN

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1. Background

Immunoglobulin A nephropathy (IgAN; Berger's disease) is the most common form of primary glomerulonephritis worldwide and is the most common cause of kidney failure in young adults[1]

IgAN is associated with a reduction in life expectancy of

10 years[2]

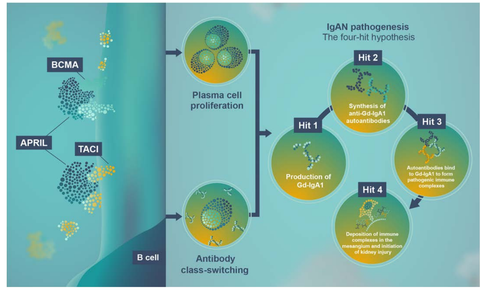
30–40%

of patients develop kidney failure within **~20 years of diagnosis**[3]

Current management comprises **antiproteinuric treatment** with renin-angiotensin aldosterone system (RAAS) blockers and adequate blood pressure control, but **the risk of kidney failure remains high**

2. Role of APRIL in IgAN

Emerging data suggest that the B-cell growth factor, A Proliferation Inducing Ligand (APRIL), plays a key role in the pathogenesis of IgAN and may be an ideal target[4]



APRIL=A Proliferation Inducing Ligand; BCMA=B-cell maturation antigen; Gd-IgA1=galactose deficient immunoglobulin A1; IgAN=Immunoglobulin A nephropathy; TACI=transmembrane activator and calcium-modulator and cyclophilin ligand.

Elevated APRIL levels are associated with poor kidney outcomes[5]

Patients with highest serum APRIL levels[5] → **10-fold** higher risk of end-stage kidney disease[5]

3. Sibeprenlimab (VIS649)

Sibeprenlimab is an investigational **anti-APRIL humanized IgG2 monoclonal antibody** engineered for the treatment of IgAN[6]

It binds and blocks the biological actions of APRIL, leading to the reduced production of IgA and Gd-IgA1[6]

4. Sibeprenlimab Clinical Development Program

PHASE 1	PHASE 2	PHASE 3	PHASE 2/3
VIS649-101[7] (VIS649-102[8])	VIS649-201 enVISion	VISIONARY	Open-label extension
NCT03719443	NCT04287985	NCT05248646	NCT05248659
COMPLETED	ONGOING	RECRUITING	RECRUITING

5. VISIONARY Phase 3 Trial Study Design

VISIONARY — Targeting a brighter future for IgAN patients.

OBJECTIVE

To evaluate the efficacy and safety of sibeprenlimab for the treatment of IgAN by measuring change from baseline in uPCR after 9 months

~470 participants will be enrolled

MULTICENTER
~300 sites
~32 countries

POWER CALCULATION

Randomization of at least 450 participants in a 1:1 ratio will provide at least 95% power to detect a 30% reduction in geometric mean of uPCR ratio at 9 months for sibeprenlimab versus placebo under a two-sided significance level of 5%

Screening → **Treatment** → **Follow-up**

SCREENING
Days −60 to −1

MAIN COHORT:
~450 participants with biopsy-confirmed IgAN, uPCR ≥0.75 g/g or 24-h urine protein ≥1.0 g/d, and eGFR ≥30 mL/min/1.73 m²

EXPLORATORY COHORT:
Up to 20 participants with biopsy-confirmed IgAN and eGFR 20–30 mL/min/1.73 m²

INTERVENTION PERIOD AND POST-TREATMENT FOLLOW-UP
Day 1 to Week 104

- Sibeprenlimab 400 mg SC q4w (n = 225)
- Placebo SC q4w (n = 225)
- Sibeprenlimab 400 mg SC q4w (n = up to 10)
- Placebo SC q4w (n = up to 10)

END OF TRIAL
Week 112

End-of-trial visit

Opportunity to enter into rollover, 24-month, open-label extension trial (NCT05248659)

RANDOMIZATION STRATIFIED BY:

1. uPCR: ≤2.0 versus >2.0 g/g
2. eGFR: 30–44 versus ≥45 mL/min/1.73 m²
3. SGLT2i use: yes or no

1 PRIMARY ENDPOINT

Ratio of uPCR at 9 months versus baseline, based on 24-h urine collection

2 SECONDARY ENDPOINTS

Key: Annualized slope of eGFR estimated over ~24 months
Other: Clinical remission rates, pharmacodynamics, safety, ADA levels

6. Study Eligibility

KEY INCLUSION CRITERIA

- ≥18 years of age
- Biopsy-confirmed IgAN
- On stable and maximally tolerated doses of ACEI or ARB for previous 3 months (or unable to tolerate these medications)
- uPCR ≥0.75 g/g or 24-h urine protein ≥1.0 g/d
- eGFR ≥30 mL/min/1.73 m²

KEY EXCLUSION CRITERIA

- Secondary form of IgAN
- Coexisting CKD, other than IgAN
- BMI <16 kg/m²
- Serum IgG value <600 mg/dL
- MEST or MEST-C score of T2 or C2
- Received systemic steroids or immunosuppressive agent within 16 weeks before screening

PERMITTED MEDICATIONS

- SGLT2i prescribed for IgAN in addition to ACEIs and/or ARBs, stable dose, and initiated ≥3 months before screening
- Medications for blood pressure control per standards of care and applicable guidelines
- Topical, ophthalmic, rectal, intra-articular, inhaled corticosteroids, or short courses (≤14 days) of oral/intravenous steroids

PROHIBITED MEDICATIONS

(16 weeks before randomization and for duration of trial)

- Agents contraindicated in IgAN per local practice (eg, chronic NSAIDs [>1 week], aminoglycosides, trimethoprim, cimetidine, pyrimethamine, fenofibrate, creatine supplements)
- Systemic corticosteroid therapy
- Other immunosuppressive therapy such as, but not limited to, mycophenolate mofetil, anti-TNF inhibitors, rituximab, hydroxychloroquine
- Traditional Chinese medicine, Ayurvedic medications, herbal supplements
- Initiation of SGLT2i, fish oil, or mineralocorticoid antagonists within 3 months of screening or at any subsequent time point during the trial

7. Participate in VISIONARY

VISIONARY — Targeting a brighter future for IgAN patients.

RECRUITING IN 32 COUNTRIES

Enroll in this trial at:

https://visionarystudy.com

For further information, email:
visionary@otsuka-us.com

ACEI=angiotensin-converting enzyme inhibitor; ADA=anti-drug antibody; ARB=angiotensin receptor blocker; BMI=body mass index; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; MEST=mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S) and interstitial fibrosis/tubular atrophy (T); NSAID=nonsteroidal anti-inflammatory drug; SC=subcutaneous; TNF=tumor necrosis factor; uPCR=urine protein/creatinine ratio; SGLT2i=sodium-glucose cotransporter-2 inhibitor.

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DISCLOSURES

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