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Comparative Network Meta-Analysis (NMA) of Sibeprenlimab Efficacy in the Treatment of Immunoglobulin A Nephropathy (IgAN)

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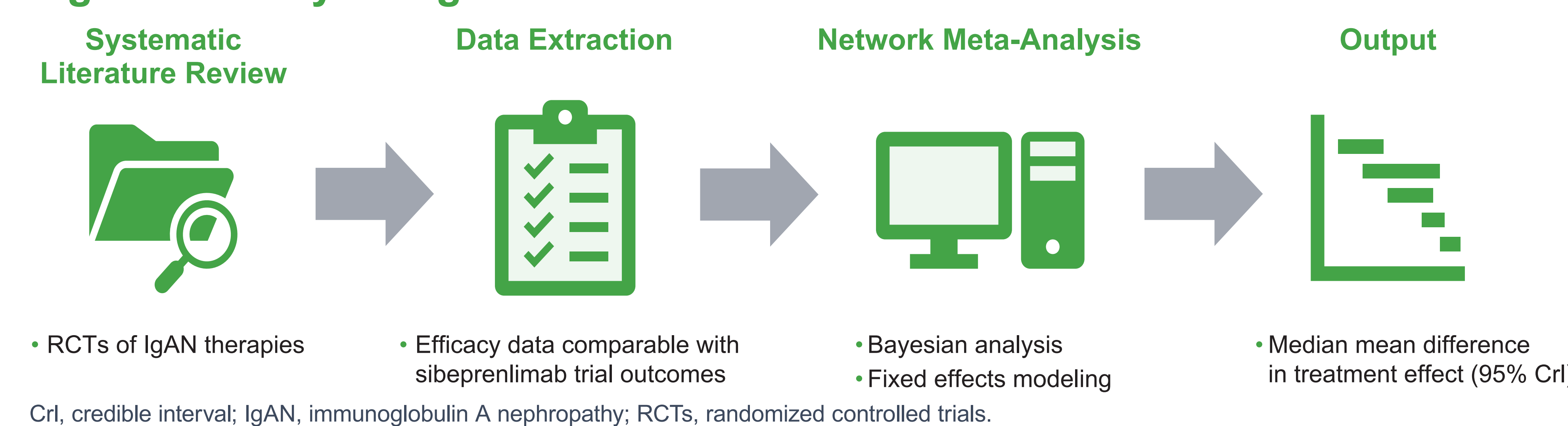
Introduction

- Immunoglobulin A nephropathy (IgAN) is an immune-mediated primary glomerulonephropathy that causes proteinuria, chronic kidney disease, and eventual kidney failure^{1,2}
- Recently, IgAN management has advanced with the approval of several disease-specific therapies and ongoing development of additional candidates³
- Sibeprenlimab is a US FDA-approved therapy for IgAN that inhibits the cytokine APRIL, which drives the formation of pathogenic immunoglobulin A1 complexes and plays a key role in IgAN pathogenesis³
- Randomized, controlled trials (RCTs) comparing all treatment options are often not possible. Network meta-analysis (NMA) enables indirect treatment comparisons by synthesizing data across trials⁴
- We conducted an NMA to assess the efficacy of sibeprenlimab relative to other US FDA-approved and investigational IgAN therapies

Methods

- This analysis was conducted in sequential steps (**Figure 1**): a systematic literature review to identify RCTs of IgAN therapies, the extraction of efficacy data, and an NMA to compare different treatments

Figure 1. Study Design



Systematic Literature Review

- Searches of Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Library were conducted up to December 2023. These were supplemented by bibliographic checks and hand searches of relevant conferences

- Targeted searches were conducted in June 2025 to capture more recent publications for key comparator trials

- An evidence map was generated to summarize trial findings

Feasibility Assessment

- RCTs of sufficient similarity in design, patient baseline characteristics, outcomes, and endpoints were selected for inclusion in the NMA, with the focus on targeted IgAN therapies

- Efficacy was assessed using urinary protein creatinine ratio (uPCR) percent change from baseline to month 9, the primary endpoint in the enVISION (Phase 2) and VISIONary (Phase 3) sibeprenlimab trials

Network Meta-Analysis

- A Bayesian NMA was performed in accordance with best practices of the National Institute for Clinical Excellence (NICE) and The Professional Society for Health Economics and Outcomes Research (ISPOR)^{5,6}

- Analyses were conducted using both fixed-effect and random-effects models. The fixed-effect model fit the data best and those results are reported
- Phase 2 and Phase 3 trials were combined in a single network to maximize the evidence base, consistent with standard practice^{5,6}
- Model assumptions included:
 - If 9-month efficacy data were not available in comparator trials, the closest timepoints were used
 - NCT03373461 (Phase 2) and APPLAUSE-IgAN (Phase 3) reported efficacy for iptacopan 200 mg at different timepoints (6 and 9 months, respectively). The data from these two trials were treated as separate treatment nodes in the network
 - The control arm for sparsentan (i.e., irbesartan 300 mg) was considered comparable to maximally tolerated/labelled/optimal renin-angiotensin-aldosterone system inhibition and was grouped in the placebo node

Model output

- Treatment effects were estimated as the median mean difference (MD) in uPCR percent change from baseline (ratio reduction), with 95% credible interval (CrI)

Results and Discussion

- Eight compounds across 11 studies with an outcome of uPCR percent change from baseline were identified for inclusion in the NMA (**Table 1**)

Table 1. Trials and Treatments Included in the Network Meta-Analysis

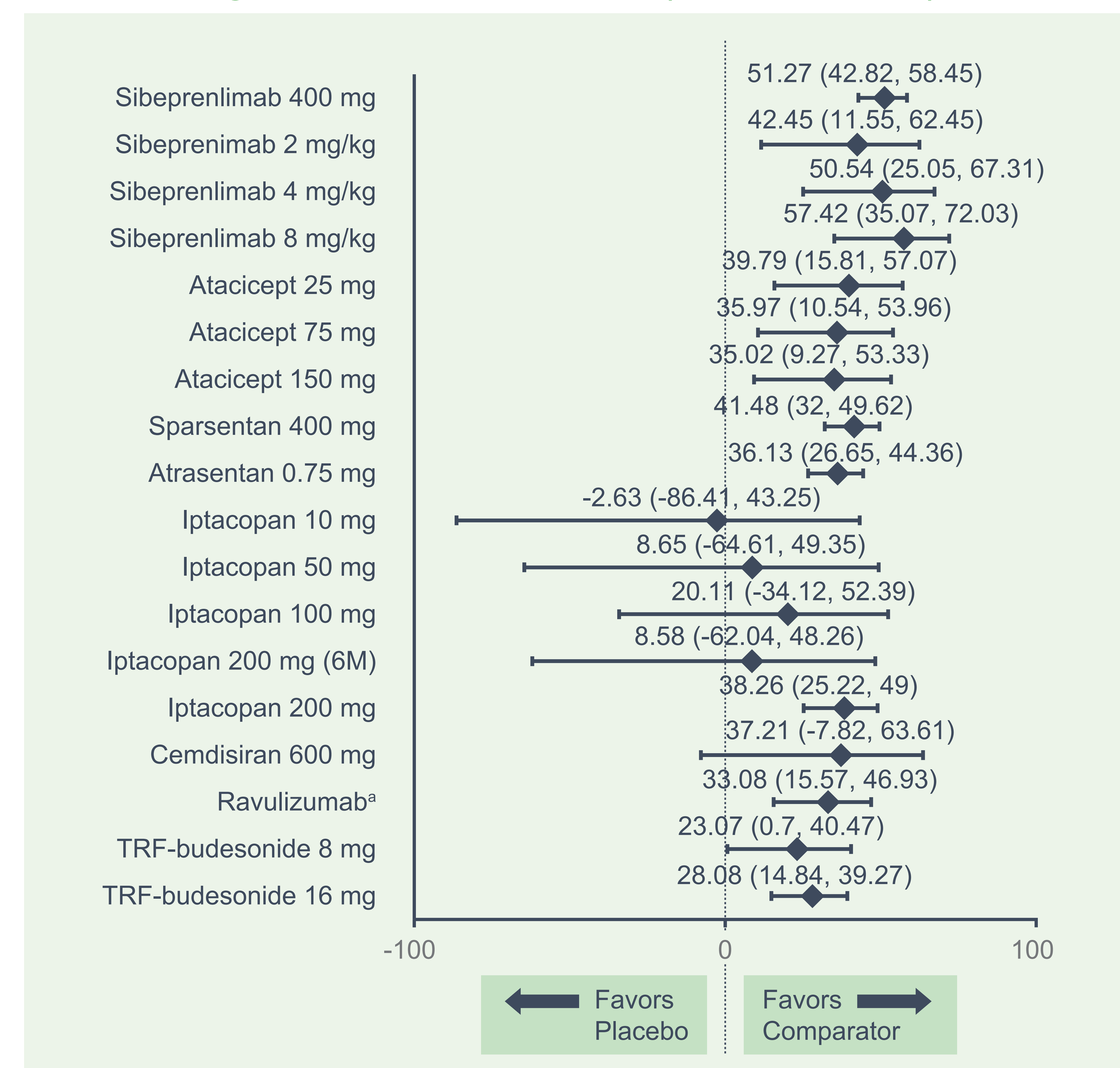
MOA	Trial	Trial Phase	Agent	Dose(s)	Timepoint for Efficacy Assessment
APRIL Inhibitor	VISIONary (NCT05248646) ^a	3	Sibeprenlimab	400 mg	9 months
	enVISION (NCT04287985)	2	Sibeprenlimab	2, 4, and 8 mg/kg	9 months
APRIL/BAFF Inhibitor	ORIGIN (NCT04716231)	2	Atacicept	25, 75, and 150 mg/kg	36 weeks
DEARA	PROTECT (NCT03762850)	3	Sparsentan	400 mg	36 weeks
ERA	ALIGN (NCT04573478)	3	Atrasentan	0.75 mg	36 weeks
Complement Inhibitor	NCT03373461	2	Iptacopan	10, 50, 100, and 200 mg	180 days
	APPLAUSE-IgAN (NCT04578834)	3	Iptacopan	200 mg	9 months
	NCT03841448	2	Cemdisiran	600 mg	32 weeks
	SANCTUARY (NCT04564339)	2	Ravulizumab	Weight-based ^b	26 weeks
Corticosteroid	NEFIGAN (NCT01738035)	2	TRF-budesonide	8 and 16 mg	9 months
	NefigArd (NCT03643965)	3	TRF-budesonide	16 mg	9 months

^aThe efficacy data from VISIONary used in this analysis were an interim dataset from this ongoing clinical trial. ^bParticipants received a weight-based loading dose on day 1 (range: 2400 to 3000 mg), followed by weight-based maintenance dosing on day 15 and then every 8 weeks (range: 3000 to 5400 mg). APRIL, A Proliferation-Inducing Ligand; BAFF, B-cell activating factor; DEARA, dual endothelin and angiotensin receptor antagonist; ERA, endothelin A receptor antagonist; MOA, mechanism of action; TRF, targeted-release formulation.

- Sibeprenlimab and most, but not all, comparators demonstrated statistically significant improvement in uPCR compared to placebo (**Figure 2**)
- Relative to other US FDA-approved comparators, sibeprenlimab 400 mg SC every 4 weeks (i.e., the Phase 3 study dose) was associated with statistically superior reduction in proteinuria versus atrasentan 0.75 mg QD (median MD = -31.01% [95% CrI -61.79, -6.19]) and TRF-budesonide 16 mg QD (median MD = -47.52% [95% CrI -86.10, -16.95]) (**Figure 3**)
- Sibeprenlimab 400 mg exhibited a directionally greater, clinically meaningful proteinuria reduction compared to other US FDA-approved treatments iptacopan 200 mg BID (measured at 9 months, median MD = -26.63% [95% CrI -62.56, 1.25]) and sparsentan 400 mg QD (median MD = -20.05% [95% CrI -49.36, 3.62])

- Longitudinal data from an IgAN cohort demonstrated that 20% to 30% greater reduction in uPCR is associated with 42% to 50% reduction in risk of kidney events (composite of a doubling of serum creatinine, kidney failure, or death)⁷
- Sibeprenlimab was statistically significantly or directionally better than all other agents

Figure 2. Median MD (95% CrI) Between Placebo and Comparators in uPCR Percent Change From Baseline to Month 9 (Ratio to Baseline)

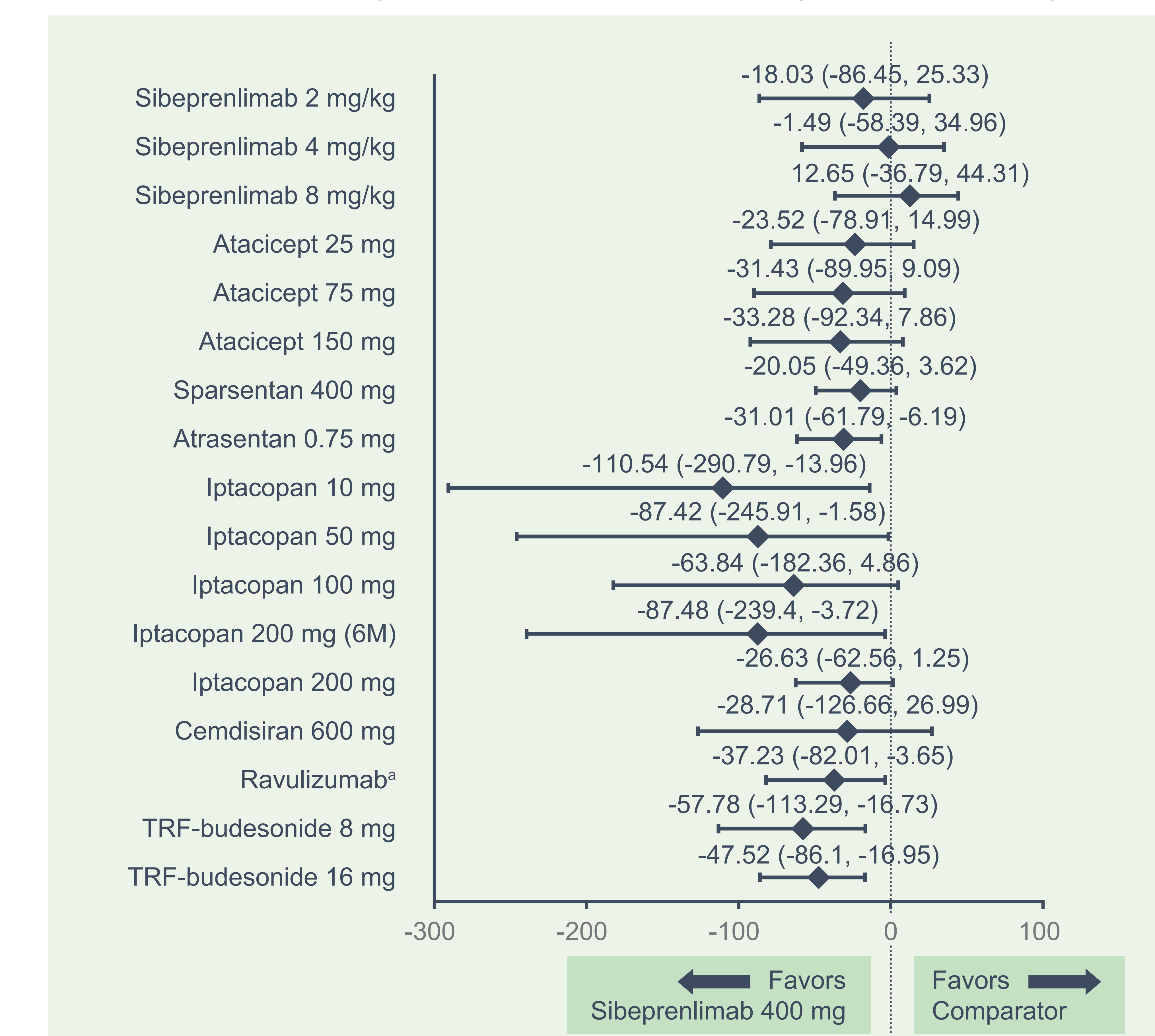


^aWeight-based dosing. CrI, credible interval; M, months; MD, mean difference; TRF, targeted-release formulation; uPCR, urine protein to creatinine ratio. The treatment difference is considered statistically significant when the 95% CrI of the difference does not cross 0.

Limitations

- Some Phase 2 trials (e.g., of iptacopan and cemdisiran) had small sample sizes, resulting in wide credible intervals for the comparisons
- Not all of the included trials reported uPCR percent change from baseline at the 9-month timepoint, therefore data had to be extracted at the closest available timepoint
- The control arm of the sparsentan trial (i.e., irbesartan) was grouped into the placebo node of the NMA, which may not fully reflect irbesartan efficacy
- Additional trial results for comparators were reported after the data searches for this analysis were completed. An updated NMA with the most recent data is planned

Figure 3. Median MD (95% CrI) Between Sibeprenlimab 400 mg and Comparators in uPCR Percent Change From Baseline to Month 9 (Ratio to Baseline)



CONCLUSIONS

- In this NMA, sibeprenlimab demonstrated clinically meaningful reductions in proteinuria relative to other US FDA-approved therapies and investigational agents
- The NMA was conducted using gold-standard methods aligned with regulatory guidance
- By integrating evidence from a systematic literature review alongside recent data from conference abstracts and key publications, the NMA provided a robust comparison with approved and investigational treatments in IgAN
- An updated NMA will be conducted when full Phase 3 results for sibeprenlimab are available

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