Supplemental Online Content

This supplemental material has been provided by the authors to give readers additional information about their work.

Supplementary Material

Heterogeneity across studies was assessed visually using graphs to depict baseline characteristics such as mean age and percentage of females. Similarly, tables were created to assess the heterogeneity qualitatively for study design, inclusion/exclusion criteria and outcome definitions across studies.

eFigure - Baseline proptosis (mm) across studies used for the meta-analysis
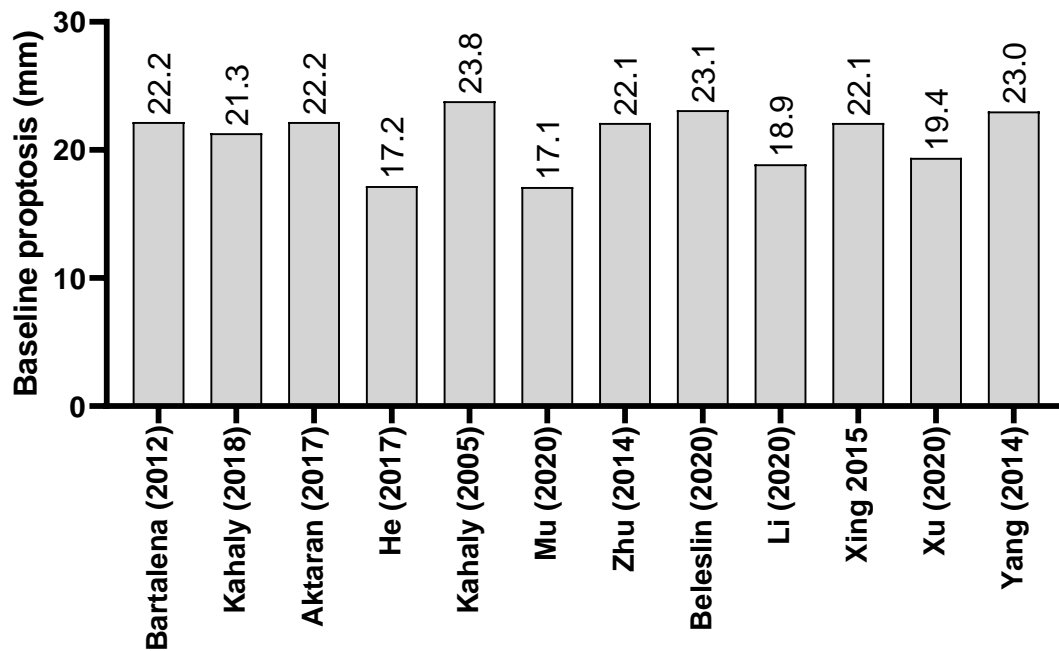
eAppendix 1: Search Strategy

Peer Review of Electronic Search Strategy (PRESS) Guideline

Systematic Review Title:

Systematic review on use of intravenous glucocorticoids for thyroid eye disease

Database

Medline and Embase.

Interface

Pubmed

Research Question

To conduct a meta-analysis on the effect of IV glucocorticoids at the EUGOGO recommended dose, on proptosis and diplopia in patients with thyroid eye disease.

To conduct an indirect treatment comparison between teprotumumab and IV glucocorticoids

PICO (Population, Intervention, Comparator, Outcome, Study Design) Format

P	Moderate-severe, active thyroid eye disease
I	IV glucocorticoids
C	Teprotumumab
O	Proptosis and diplopia
S	Any

- All ages
- All study designs
- IV methylprednisolone 4.5g (0.5 g weekly for 6 weeks followed by 0.25g weekly for 6 weeks)
- Proptosis and/or diplopia results at 12 weeks
- English
- Patients with moderate-severe active thyroid eye disease

Inclusion Criteria

Exclusion Criteria

- Patients without thyroid eye disease
- IV methylprednisolone at other doses
- Results at 12 weeks not reported
- Other languages

No search filter applied

Other notes or comments

The search strategy conducted in Pubmed: ((methylprednisolone) OR (intravenous steroid)) AND

((((((thyroid eye disease) OR (graves ophthalmopathy)) OR (endocrine ophthalmopathy)) OR (graves

orbitopathy)))

eAppendix 2: PRISMA Flow Diagram

PRISMA 2009 Flow Diagram
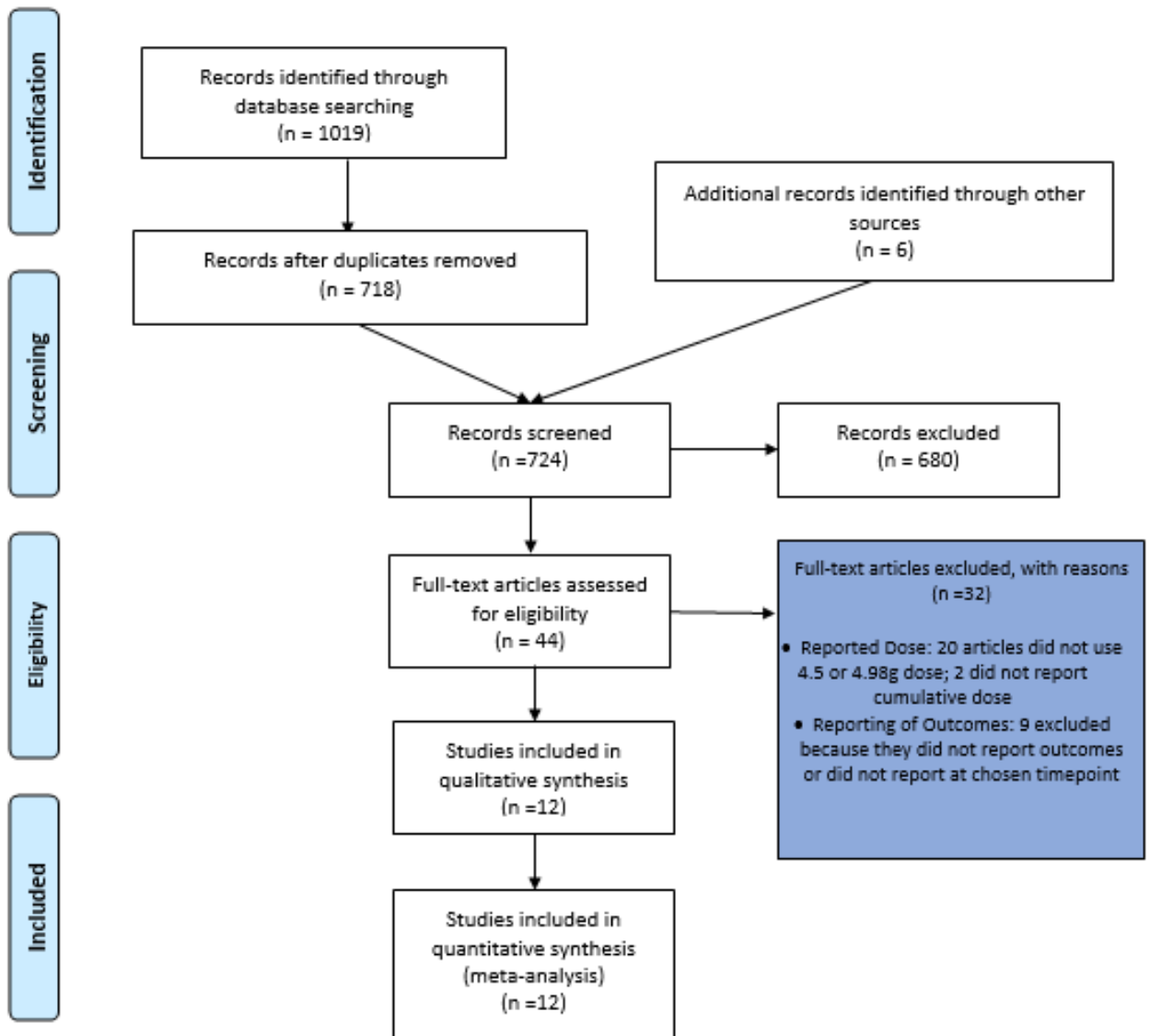
Identification

Records identified through database searching
(n = 1019)

Additional records identified through other sources
(n = 6)

Screening

Records after duplicates removed
(n = 718)

Records screened
(n =724)

Records excluded
(n = 680)

Eligibility

Full-text articles assessed for eligibility
(n = 44)

Full-text articles excluded, with reasons
(n =32)

- Reported Dose: 20 articles did not use 4.5 or 4.98g dose; 2 did not report cumulative dose
- Reporting of Outcomes: 9 excluded because they did not report outcomes or did not report at chosen timepoint

Included

Studies included in qualitative synthesis
(n =12)

Studies included in quantitative synthesis (meta-analysis)
(n =12)

eAppendix 3: MAICs for Teprotumumab versus IVMP

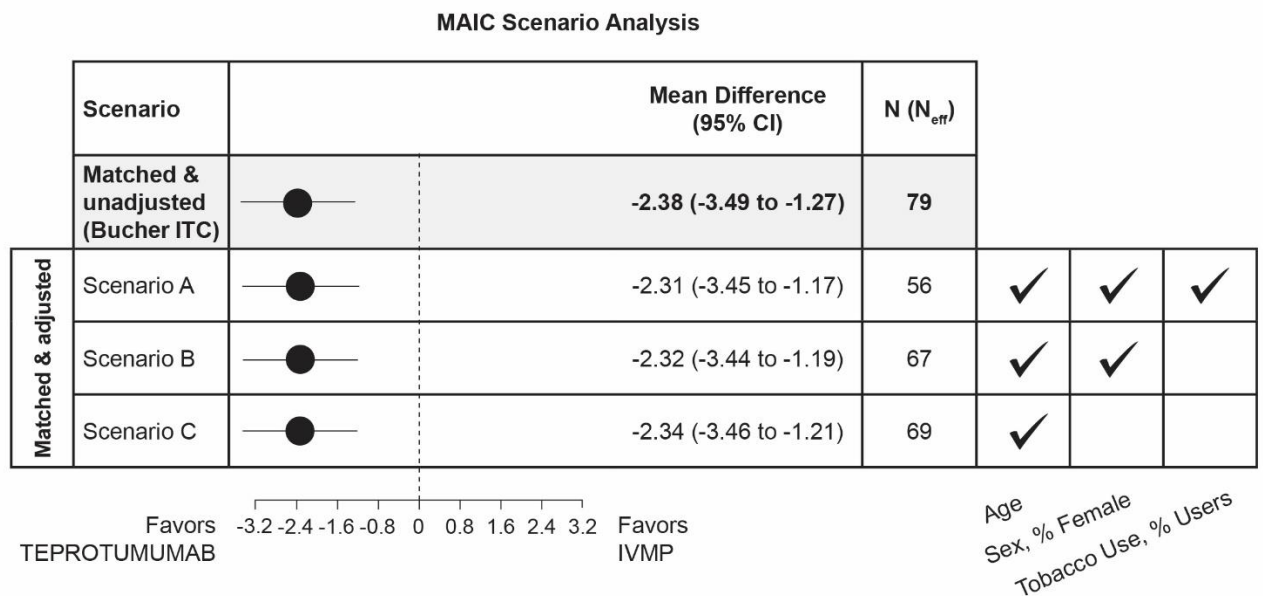## Change from baseline in proptosis (mm)

N_{eff}, pre-match, and post-match characteristics

Variables	Published Data	Teprotumumab (Matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (N_{eff})	**419**	**79**	56	67	69
Age, Mean (SD)	**47.12 (9.72)**	**51.44 (11.55)**	47.12 (9.79)	47.12 (9.79)	47.12 (9.79)
Sex, % Female	**62.66%**	**70.89%**	62.66%	62.66%	
Tobacco Use, % Users	**44.72%**	**24.05%**	44.72%		

Abbreviations: N_{eff} = effective sample size; SD = standard deviation

MAIC Scenario Analysis

Scenario		Mean Difference (95% CI)	N (N_{eff})	Age	Sex, % Female	Tobacco Use, % Users
Matched & unadjusted (Bucher ITC)		-2.38 (-3.49 to -1.27)	79			
Scenario A		-2.31 (-3.45 to -1.17)	56	✓	✓	✓
Scenario B		-2.32 (-3.44 to -1.19)	67	✓	✓	
Scenario C		-2.34 (-3.46 to -1.21)	69	✓		

Favors TEPROTUMUMAB   -3.2 -2.4 -1.6 -0.8 0 0.8 1.6 2.4 3.2   Favors IVMP

Abbreviations: CI: confidence interval; ITC: indirect treatment comparison; IV: intravenous MAIC: matching adjusted indirect comparison; N_{eff} = effective sample size; SD = standard deviation

Diplopia response

N$_{eff}$, pre-match, and post-match characteristics

Variables	Published Data	Teprotumumab (Matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (N$_{eff}$)	**125**	**63**	44	60	61
Age, Mean (SD)	**48.81 (11.06)**	**51.28 (11.31)**	48.81 (11.15)	48.81 (11.15)	48.81 (11.15)
Sex, % Female	**66.22%**	**69.84%**	66.24%	66.22%	
Tobacco Use, % Users	**52.11%**	**25.4%**	52.51%		

Abbreviations: Neff =effective sample size; SD = standard deviation

MAIC Scenario Analysis

Scenario	Odds Ratio (95% CI)	N (N$_{eff}$)	Age	Sex, % Female	Tobacco Use, % Users
Matched & unadjusted (Bucher ITC)	2.75 (1.42 to 5.31)	63			
Scenario A	2.32 (1.07 to 5.03)	44	✓	✓	✓
Scenario B	2.71 (1.37 to 5.34)	60	✓	✓	
Scenario C	2.78 (1.41 to 5.49)	61	✓		

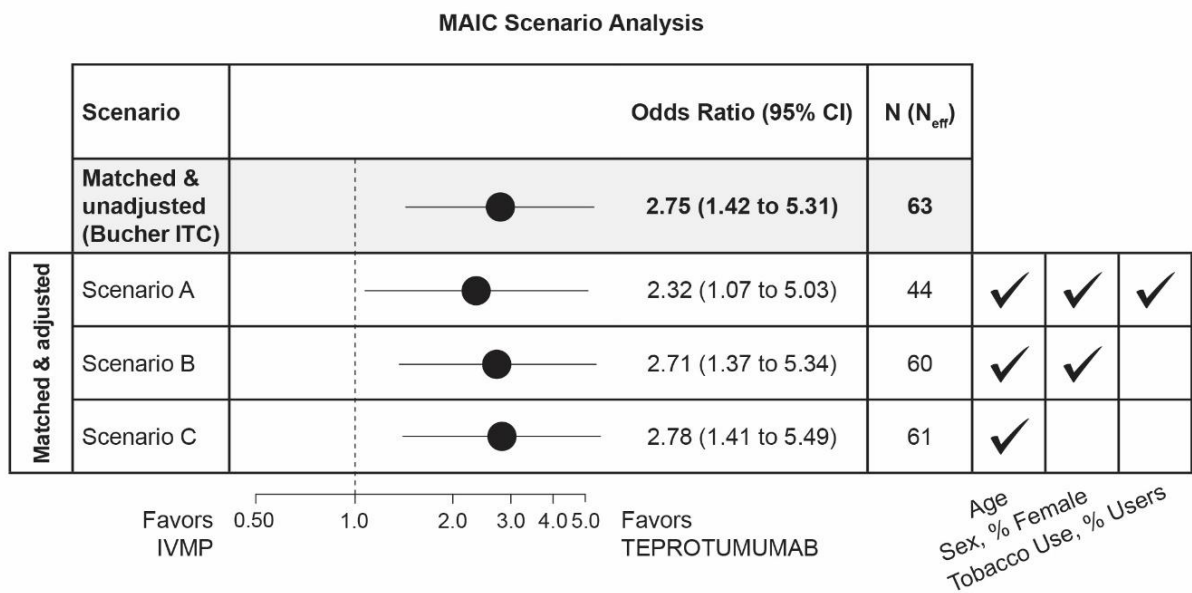Favors IVMP 0.50 1.0 2.0 3.0 4.0 5.0 Favors TEPROTUMUMAB

Abbreviations: CI: confidence interval; ITC: indirect treatment comparison; IV: intravenous MAIC: matching adjusted indirect comparison; N$_{eff}$ = effective sample size; SD = standard deviation
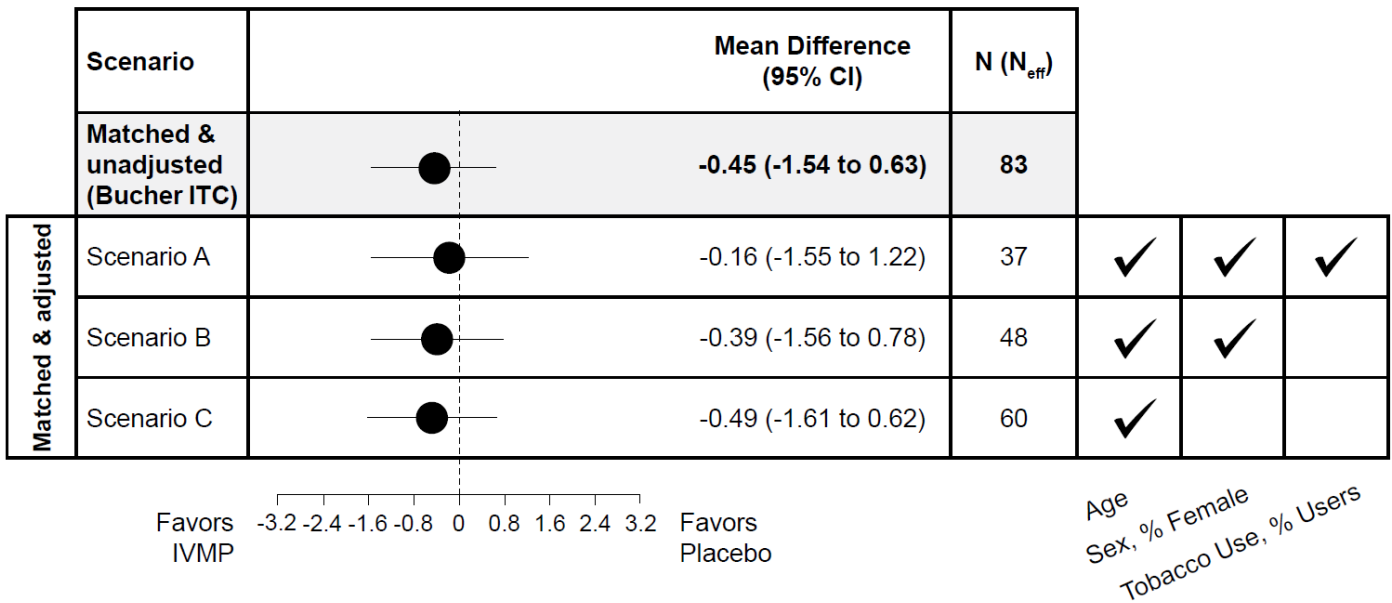
eAppendix 4: MAICs for IVMP versus Placebo

Change from baseline in proptosis (mm)

N$_{eff}$, pre-match, and post-match characteristics

Variables	Published Data	Placebo (Matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (N$_{eff}$)	**419**	**83**	37	48	60
Age, Mean (SD)	**47.12 (9.72)**	**51.95 (13.21)**	47.12 (9.81)	47.12 (9.8)	47.12 (9.79)
Sex, % Female	**62.66%**	**79.52%**	62.66%	62.66%	
Tobacco Use, % Users	**44.72%**	**28.92%**	44.72%		

Abbreviations: Neff =effective sample size; SD = standard deviation

MAIC Scenario Analysis

Scenario	Mean Difference (95% CI)	N (N$_{eff}$)	Age	Sex, % Female	Tobacco Use, % Users
Matched & unadjusted (Bucher ITC)	**-0.45 (-1.54 to 0.63)**	83			
Scenario A	-0.16 (-1.55 to 1.22)	37	✓	✓	✓
Scenario B	-0.39 (-1.56 to 0.78)	48	✓	✓	
Scenario C	-0.49 (-1.61 to 0.62)	60	✓		

Favors IVMP -3.2 -2.4 -1.6 -0.8 0 0.8 1.6 2.4 3.2 Favors Placebo

Abbreviations: CI: confidence interval; ITC: indirect treatment comparison; IV: intravenous MAIC: matching adjusted indirect comparison; N$_{eff}$ = effective sample size; SD = standard deviation
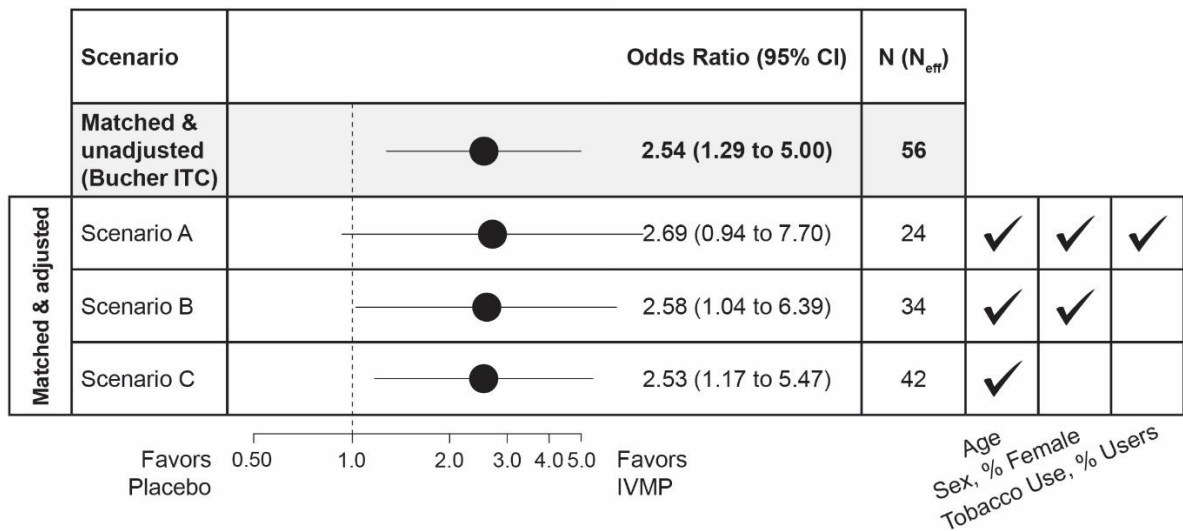
Diplopia response

N$_{eff}$, pre-match, and post-match characteristics

Variables	Published Data	Placbeo (Matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (N$_{eff}$)	**125**	**56**	24	34	42
Age, Mean (SD)	**48.81 (11.06)**	**52.32 (13.9)**	48.81 (11.24)	48.81 (11.19)	48.81 (11.18)
Sex, % Female	**66.22%**	**80.36%**	66.23%	66.22%	
Tobacco Use, % Users	**52.11%**	**28.57%**	52.1%		

Abbreviations: N$_{eff}$ =effective sample size; SD = standard deviation

MAIC Scenario Analysis

Scenario	Odds Ratio (95% CI)	N (N$_{eff}$)	Age	Sex, % Female	Tobacco Use, % Users
Matched & unadjusted (Bucher ITC)	2.54 (1.29 to 5.00)	56			
Scenario A	2.69 (0.94 to 7.70)	24	✓	✓	✓
Scenario B	2.58 (1.04 to 6.39)	34	✓	✓	
Scenario C	2.53 (1.17 to 5.47)	42	✓		

Matched & adjusted

Favors Placebo   0.50   1.0   2.0   3.0 4.0 5.0   Favors IVMP

Abbreviations: CI: confidence interval; ITC: indirect treatment comparison; IVMP: intravenous methylprednisolone; MAIC: matching adjusted indirect comparison; N$_{eff}$ = effective sample size; SD = standard deviation