The efficacy and safety of Brolucizumab for neovascular age-related macular degeneration (AMD): A Systematic Review and Meta-analysis

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Background. To evaluate the efficacy and safety of Brolucizumab for neovascular age-related macular degeneration (n-AMD) by systematic review and meta-analysis.

Materials and Methods. A comprehensive electronic search was conducted in Cochrane, PubMed, Embase, and Web of Science databases for relevant studies. Stata and RevMan5.4 were used for meta-analysis and bias risk assessment, respectively. Data on the best-corrected visual acuity (BCVA), central subfield thickness (CSFT), presence of intraretinal (IRF) and/or subretinal fluid (SRF), participants with ≥1 serious adverse events, and participants with ≥1 adverse events were analyzed.

Results. Six studies were included. According to the meta-analysis, there were statistical differences in BCVA [SMD=-0.65, 95%CI (-0.17, -0.23)], the presence of intraretinal (IRF) and/or subretinal fluid (SRF) [RR=0.67, 95%CI (0.56, 0.79)] and the safety of participants with ≥1 serious adverse events [RR=0.57, 95%CI (0.39, 0.84)] between the experimental group and the control group. However, no statistical differences were observed in CSFT [SMD=-1.16, 95%CI (-2.79, 0.47)] or the safety of participants with ≥1 adverse events [RR=1.07, 95%CI (0.97, 1.17)].

Conclusions. Compared to other anti-VEGF drugs such as Aflibercept and Ranibizumb, intravitreal injection of 6mg Brolucizumab for neovascular AMD is more effective and safe in the treatment of n-AMD, especially in the presence of IRF and/or SRF, and on participants with ≥1 serious adverse events.

1 **The efficacy and safety of Brolucizumab for neovascular age-related macular degeneration**

2 **(AMD): A Systematic Review and Meta-analysis**

4 **Running title:** Safety & efficacy of Brolucizumab

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14 **Abstract**

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16 macular degeneration (n-AMD) by systematic review and meta-analysis.

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24   differences in BCVA [SMD=-0.65, 95%CI (-0.17, -0.23)], the presence of intraretinal (IRF) and/or

25   subretinal fluid (SRF) [RR=0.67, 95%CI (0.56, 0.79)] and the safety of participants with ≥1 serious

26   adverse events [RR=0.57, 95%CI (0.39, 0.84)] between the experimental group and the control

27   group. However, no statistical differences were observed in CSFT [SMD=-1.16, 95%CI (-2.79,

28   0.47)] or the safety of participants with ≥1 adverse events [RR=1.07, 95%CI (0.97, 1.17)].

29   **Conclusions.** Compared to other anti-VEGF drugs such as Aflibercept and Ranibizumb,

30   intravitreal injection of 6mg Brolucizumab for neovascular AMD is more effective and safe in the

31   treatment of n-AMD, especially in the presence of IRF and/or SRF, and on participants with ≥1

32   serious adverse events.

33

34   **Keywords**: AMD; anti-VEGF; Brolucizumab; Meta-analysis; Aflibercept; Ranibizumb

35

36   **Introduction**

37   As we all know, neovascular age-related macular degeneration (n-AMD) is one of the most

38   common causes of blindness (1-3). Current treatment guidelines suggest intravitreal injection of

39   anti-vascular endothelial growth factor (VEGF) agents has become the first-line therapy for n-

40   AMD over the last decade (4, 5). Currently, main agents includes ranibizumab (Lucentis;

41   Genentech, South San Francisco, CA, USA) (6, 7) and afibercept (Eylea; Regeneron, Tarrytown,

42   NY, USA, and Bayer HealthCare, Berlin, Germany) (8). It is reported that anti-VEGF drugs, such

43   as Aflibercept and Ranibizumb, are effective and safe in the treatment of n-AMD (3, 9-11). Based

44   on safety and efficacy studies of the intravitreal injection of anti-VEGF drugs, Brolucizumab as a

45   new anti-VEGF drug bring us a brand new page on treating n-AMD.

46   Brolucizumab is a humanized single-chain antibody fragment that consists of the tips of the Fab

47   region of the antibody, linked by a peptide linker. Alike ranibizumab, brolucizumab inhibits all

48   isoforms of VEGF-A. Therefore, we conducted this meta-analysis to analyze the differences in the

49   efficacy and safety between this new drug, Brolucizumab, and other anti-VEGF drugs, in the

50   treatment of n-AMD (12-18).

51   Furthermore, exploring the efficacy and safety of Brolucizumab (1, 19), which is a new

52   monoclonal antibody anti-VEGF drug for the treatment of n-AMD, is even more meaningful than

53   other anti-VEGF drugs (1, 4, 12, 19).

54   Although several reticular meta-analyses have been conducted to compare the efficacy of

55   Brolucizumab with other anti-VEGF drugs, no meta-analysis has been published regarding the

56   safety and efficacy of this monoclonal antibody (20, 21). Hence, we conducted this meta-analysis

57   to analyze the safety and efficacy of Brolucizumab in the treatment of n-AMD, so as to provide a

58   reference for the clinical treatment of this condition.

59

60   **Materials and Methods**

61   This meta-analysis was registered with the International Prospective Register of Systematic

62   Reviews (PROSPERO) (CRD42023389716).

63   ***Literature search***

64   Relevant studies were retrieved from foreign databases, including Cochrane, PubMed, Embase,

65   and Web of Science. According to the "PICO" retrieval strategy, the English search words,

66   "Brolucizumab" and "Macular Degeneration", were used. All studies were retrieved with a

67   combination of subject headings and free words, and the reference lists of the included studies

68   were also manually searched to avoid missing eligible studies. The search strategy (performed by

69   Ran Dou and Jian Jiang who served as screeners) is described in Table S1. And Dongchang Zhang

70 took place of referee. However, there were no disagreements between the screeners.

71 ***Inclusion and exclusion criteria***

72 *Inclusion criteria*

73 1) Patients: patients were diagnosed with n-AMD;

74 2) Intervention: the experimental groups were treated with the introvitreal Brolucizumab;

75 3) Comparison: the control groups were treated with the introvitreal injection of other anti-VEGF

76 drugs, including Aflibercept or Ranibizumb, which are recognized as effective drugs for AMD.

77 4) Outcomes: the primary outcome measures included best-corrected visual acuity (BCVA) and

78 central subfield thickness (CSFT), while the secondary outcomes were the presence of IRF and/or

79 SRF, presence of sub-RPE fluid, participants with ≥1 serious adverse events, and participants with

80 ≥1 adverse events.

81 5) Study type: randomized controlled trials (RCTs).

82 *Exclusion criteria*

83 1) Animal experiments, meta-analyses, meeting abstracts, letters, or systematic reviews;

84 2) Duplicate literature or suspected plagiarism;

85 3) The original passages were unobtainable;

86 4) Data of interest were unobtainable;

87 5) Non-English literature.

88 ***Data Extraction***

89 Two researchers (Ran Dou and Jian Jiang) independently screened the literature according to the

90 inclusion and exclusion criteria. Then they extracted relevant data and cross-checked their results.

91 Extracted data included basic information about the selected studies (e. g., title, first author, journal

92 publication time, region), intervention measures of the control group and the experimental group,

93 major elements of the risk of bias assessment, and outcome measures of interest.

94 *Quality evaluation*

95 According to the Risk of Bias Assessment tool of Cochrane Collaboration, two investigators (Ran

96 Dou and Jian Jiang) assessed the risk of bias in the included studies. The assessment includes 7

97 items: random allocation method, allocation scheme hiding, blinding of the research objects and

98 personnel, blinding of the outcome measures, integrity of the outcome data, selective reporting,

99 and other bias. Each item can be evaluated as "low risk," "high risk," or "unclear."

100 *Statistical Analysis*

101 The STATA software was used for the meta-analysis, and the RevMan software provided by the

102 Cochrane Collaboration was used for bias assessment.

103 Because the doses used in the experimental groups were different, subgroup analysis was

104 performed according to 6mg Brolucizumab and <6mg Brolucizumab. In this meta-analysis,

105 standardized mean difference (SMD) and relative risk (RR)was used as the effect sizes, and a 95%

106 confidence interval (CI) was provided for each effect size. Q-test was used for qualitative analysis,

107 and the I^2 statistic was used to quantify the heterogeneity. When P>0.1 and $I^2 \leq 50\%$, the

108 homogeneity among the studies was considered, and a fixed-effects model was used for meta-

109 analysis. If P≤0.1, I^2>50%, and no clinical heterogeneity was determined, a random-effects model

110 was used for meta-analysis. If clinical heterogeneity was found, subgroup analysis or sensitivity

111 analysis was used to explore the source of heterogeneity.

112

113 **Results**

114 *Literature search process and results*

115 According to the retrieval strategy, a total of 511 studies were obtained. After the duplicates were

116   removed, 322 studies remained. After reading the titles and abstracts, 290 ineligible articles were

117   excluded. Based on a full-text-review, 6 studies were included. The basic characteristics of the

118   included studies are shown in Figure 1.

119   ***Basic characteristics table of the included literature***

120   The 6 included studies (12-17)were all RCTs. The intervention for the experimental group was

121   intravitreal injection of Brolucizumab, while the intervention for the control group was intravitreal

122   injection of other anti-VEGF drugs, such as Aflibercept and Ranibizumb. (show in Table 1)

123   ***Offset risk assessment chart***

124   All 6 included studies (12-17) were randomized, double-masked, multicentre clinical trials. All the

125   included studies mentioned the allocation concealment, the blinding of the researchers and

126   subjects, as well as the blinding of the evaluators (Figure 2, Figure 3).

127   ***Meta-analysis results***

128   *BCVA*

129   As shown in the forest plot, the prismatic figure of indicator fell to the left of the invalid line and

130   did not intersect with the invalid line in the Brolucizumab group. The results showed that the

131   intravitreal injection of Brolucizumab had a worse effect on BCVA than the control [SMD=-0.65,

132   95%CI (-0.17, -0.23)], and the difference was statistically significant. (show in Figure 4)

133   As shown in the forest plot for subgroup analysis, the prismatic figure of the indicator fell to the

134   left of the invalid line and intersected with the invalid line in the experimental subgroup treated

135   with 6mg of Brolucizumab. The results showed that no significant difference was present between

136   the subgroup of 6mg Brolucizumab and the control group [SMD=-0.50, 95%CI (-1.19, -0.20)]. In

137   the experimental subgroup treated with <6mg of Brolucizumab, the prismatic figure of the

138   indicator fell to the right of the invalid line and did not intersect with the invalid line. The results

139 showed that there were differences between the experimental subgroup of <6mg Brolucizumab

140 and the control group [SMD=-099, 95%CI (-1.14, -0.84)].

141 Sensitivity analysis was performed. The results showed that the data were distributed within the

142 interval, indicating that the analysis results were stable.

143 *CSFT*

144 As shown in the forest plot, the prismatic figure of the indicator intersected with the invalid line

145 in the experimental group. The results showed that there was no statistical difference between the

146 experimental group and the control group [SMD=-1.16, 95%CI (-2.79, 0.47)]. (show in Figure 5)

147 As shown in the forest plot for subgroup analysis, in the experimental subgroups treated with both

148 6mg Brolucizumab and <6mg Brolucizumab, the prismatic figure of the indicator intersected with

149 the invalid line. The results showed that there was no statistical difference between the

150 experimental subgroup and the control group [6mg Brolucizumab: SMD=-2.52, 95%CI (-6.05,

151 1.00); <6mg Brolucizumab: SMD=-0.38, 95%CI (-1.98, 1.23)].

152 Sensitivity analysis was performed. The results showed that the data were distributed within the

153 interval, indicating that the analysis results were stable.

154 *Presence of IRF and/or SRF (F3)*

155 As shown in the forest plot, in the experimental group, the prismatic figure of the indicator fell to

156 the left of the invalid line and did not intersect with the invalid line. The results showed that there

157 were statistical differences between the experimental group and the control group [RR=0.67,

158 95%CI (0.56, 0.79)].

159 Sensitivity analysis was performed. The results showed that the data were distributed within the

160 interval, indicating that the analysis results were stable. (show in Figure 6)

161 *Participants with ≥1 serious adverse events (F5)*

162 As shown in the forest plot, in the experimental group, the prismatic figure of the indicator

163 intersected with the invalid line. The results showed that there were statistical differences between

164 the experimental group and the control group [RR=0.57, 95%CI (0.39, 0.84)].

165 As shown in the forest plot for subgroup analysis, in the experimental subgroup treated with 6mg

166 of Brolucizumab, the prismatic figure of the indicator fell to the left of the invalid line and did not

167 intersect with the invalid line. The results showed that there were statistical differences between

168 the experimental group of 6mg Brolucizumab and the control group [RR=0.51, 95%CI (0.28,

169 0.92)]. In the subgroup treated with <6mg of Brolucizumab, the prismatic figure of the indicator

170 fell to the left of the invalid line and intersected with the invalid line. The results showed that no

171 statistical differences were observed between the experimental group of <6mg Brolucizumab and

172 the control group [RR=0.72, 95%CI (0.53, 0.97)].

173 Sensitivity analysis was performed. The results showed that the data were distributed within the

174 interval, indicating that the analysis results were stable. (show in Figure 7)

175 *Participants with ≥1 adverse events (F6)*

176 As shown in the forest plot, in the experimental group, the prismatic figure of the indicator fell to

177 the right of the invalid line and intersected with the invalid line. The results showed that there was

178 no statistical difference between the experimental group and the control group [RR=1.07, 95%CI

179 (0.97, 1.17)].

180 As shown in the forest plot for subgroup analysis, in the experimental subgroup, the prismatic

181 figure of the indicator fell to the right of the invalid line, and intersected with the invalid line. The

182 results showed that there was no statistical difference between the experimental subgroup and the

183   control group [6mg Brolucizumab: RR=1.06, 95%CI (0.91, 1.23); <6mg Brolucizumab: RR=1.07,

184   95%CI (0.95, 1.26)].

185   Sensitivity analysis was performed. The results showed that the data were distributed within the

186   interval, indicating that the analysis results were stable. (show in Figure S1)

187   *Evaluation of Publication Bias*

188   The outcome measures of this study were BCVA, CSFT, presence of IRF and/or SRF, participants

189   with ≥1 serious adverse events, and participants with ≥1 adverse events. Therefore, funnel plots

190   were drawn for the outcome measures. It was visually observed that the scattered distribution on

191   both sides of the funnel plots was asymmetric, indicating the presence of publication bias. (show

192   in Figure S2)

193

194   **Discussion**

195   In this study, meta-analysis was used to evaluate the effects and safety of different anti-VEGF

196   drugs on n-AMD. 6 studies (21-26) were included and evaluated the efficacy and safety based on

197   BCVA, CSFT, presence of IRF and/or SRF, participants with ≥1 serious adverse events, and

198   participants with ≥1 adverse events (4, 27, 28). Subgroup analysis was performed according to

199   different doses of Brolucizumab.

200   Safety of Brolucizumab is the primary consideration in clinical medication. Three studies (21, 24,

201   25) reported the safety of participants with ≥1 adverse events, and the meta-analysis showed that

202   there was no statistical difference between the experimental group and the control group. This

203   indicates that intravitreal injection of Brolucizumab is as safe as other anti-VEGF drugs in

204   participants with ≥1 adverse events. In addition, the meta-analysis results of five studies (23-26,

205   29) showed that intravitreal injection of 6mg Brolucizumab ended in better results regarding the

206   safety (30) of participants with ≥1 serious adverse events. That is to say, brolucizumab is as safe

207   as other anti-VEGF drugs for n-AMD, especially for those with serious adverse events, which

208   provides us with a safe guarantee for clinical application.

209   On the premise that safety is not inferior to other anti-VEGF drugs, effectiveness analysis has

210   become the most important indicator of clinical medication. It is well known that BCVA, CSFT

211   and presence of IRF and/or SRF are the basis for judging whether Brolucizumab is effective or not

212   in the treatment of n-AMD. The meta-analysis results of three studies (22, 25, 26) reported on

213   BCVA showed that the intravitreal injection of 6mg Brolucizumab had the same efficacy as the

214   control, althougth other concentrations used in the experimental groups showed a poorer effect.

215   Therefore, in order to obtain the same BCVA as aflibercept, Brolucizumab at a dose of 6mg should

216   be administered. As regards CSFT, the meta-analysis results showed that Brolucizumab did not

217   have superiority (31, 32). Brolucizumab did not outperform the control agents in CSFT. Then if a

218   concentration of >6mg Brolucizumab was used, could it be better on the BCVA and CSFT Under

219   the premise of non-inferior safety to other anti-VEGF drugs? Which dose would be the best? This

220   may be explored further in the future.

221   The meta-analysis results showed that intravitreal injection of Brolucizumab had a better effect

222   than aflibercept on the presence of IRF and/or SRF. In treatment cases, we found that the

223   Brolucizumab group showed better results than the control group on morphology. Furthermore,

224   about the molecule characteristics, just like ranibizumab, Brolucizumab inhibits VEGF-A alone.

225   However, because of its low molecular weight and high stability and solubility, it can be highly

226   concentrated and administered in molar doses 12 times higher than that of afibercept, and 22 times

227   higher than that of ranibizumab (19). The anatomical impact of such high-dose administration of

228   Brolucizumab on the choroid might result in a more successful resolution of SRF and IRF.

229   Combined with the above-mentioned effects on BCVA and CSFT, although the drug is able to be

230   accumulated in high concentrations, it did not show superiority in reducing CSFT, despite its

231   excellent morphological performance. In brief, if brolucizumab could play a better role in CSFT,

232   it may have a more impressive curative effect.

233   In the global phase III HAWK and HARRIER trials, intravitreal injections of Brolucizumab every

234   3 months after the loading phase yielded visual outcomes similar to those of intravitreal afibercept

235   injections administered every 2 months (19), which is a more convenient and cheaper choice for

236   the patients with n-AMD. Brolucizumab might bring much better therapeutic effects for clinical

237   treatments. However, the evaluation indicators of the included studies were different, and the

238   sample sizes of the same outcome indicators were limited. Therefore, the results of this meta-

239   analysis should be interpreted carefully. Also, the scope of this study was limited to English papers,

240   and some high-quality studies reported in other languages may be ignored. More large-sample,

241   multicenter, and high-quality clinical studies are needed to demonstrate the efficacy and safety of

242   Brolucizumab.

243

244   **Conclusions**

245   Compared to other anti-VEGF drugs such as Aflibercept and Ranibizumb, intravitreal injection of

246   6mg Brolucizumab for neovascular AMD is more effective and safe in the treatment of n-AMD,

247   especially in the presence of IRF and/or SRF, and on participants with ≥1 serious adverse events.

248

249   **Declarations**

250   **Availability of data and materials**

251   Data sharing not applicable to this article as no datasets were generated or analysed during the

252 current study.

Conflict of interest

254 The authors declared no competing interests.

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257

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367

368 **Tables**

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390

391 **Supplementary materials**

392 **Table S1** PubMed Search History

393 **Figure S1** Sensitivity analysis. (a) Meta-analysis for the participants with ≥1 adverse event

394 between the experimental group and the control group; (b) Meta-analysis for the participants with

395 ≥1 adverse event between the experimental subgroup and the control group; (c) Sensitivity analysis

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Figure 1

PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic review and Meta-analysis

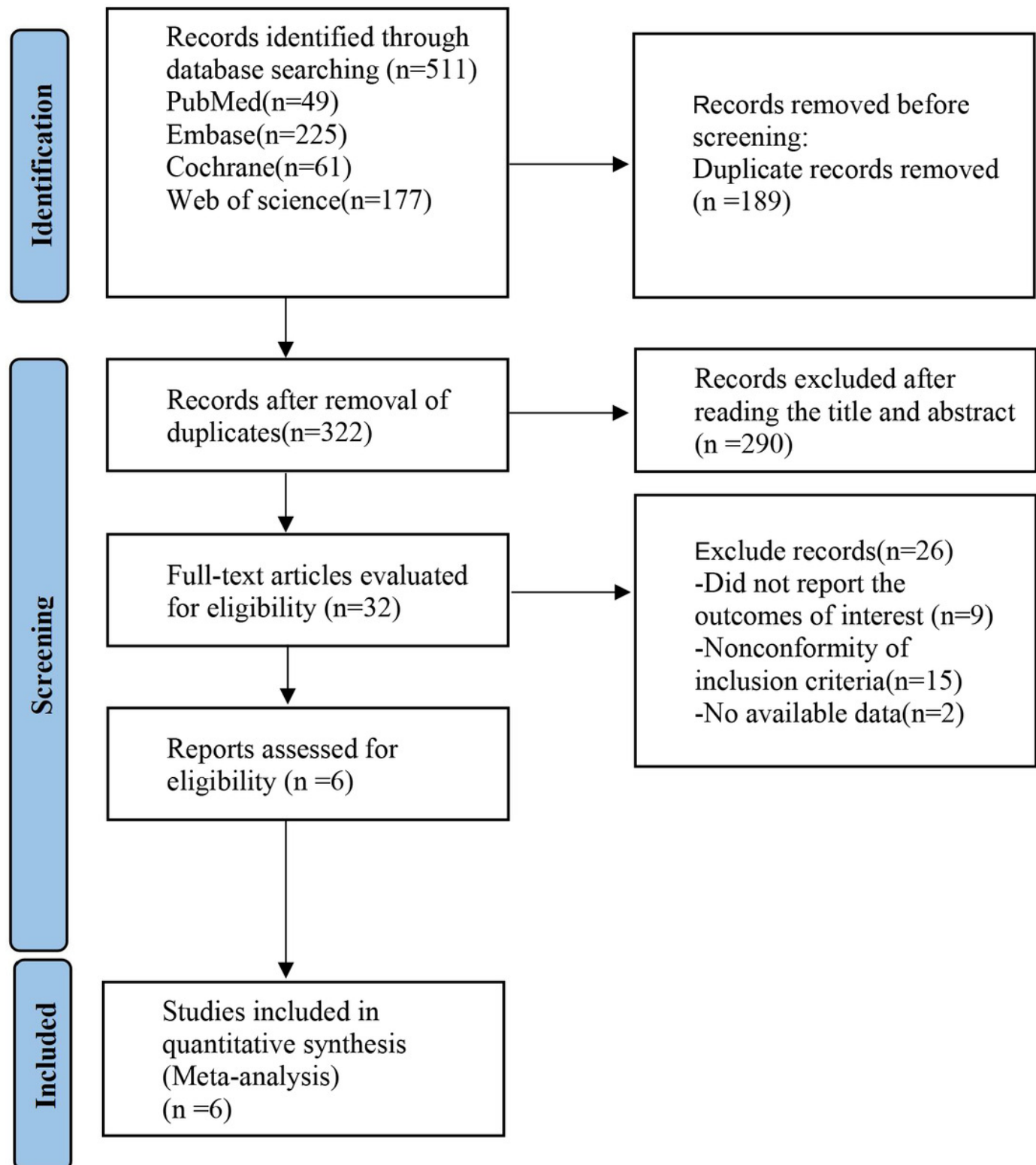



Figure 2

Risk of bias graph of all the retrieved studies

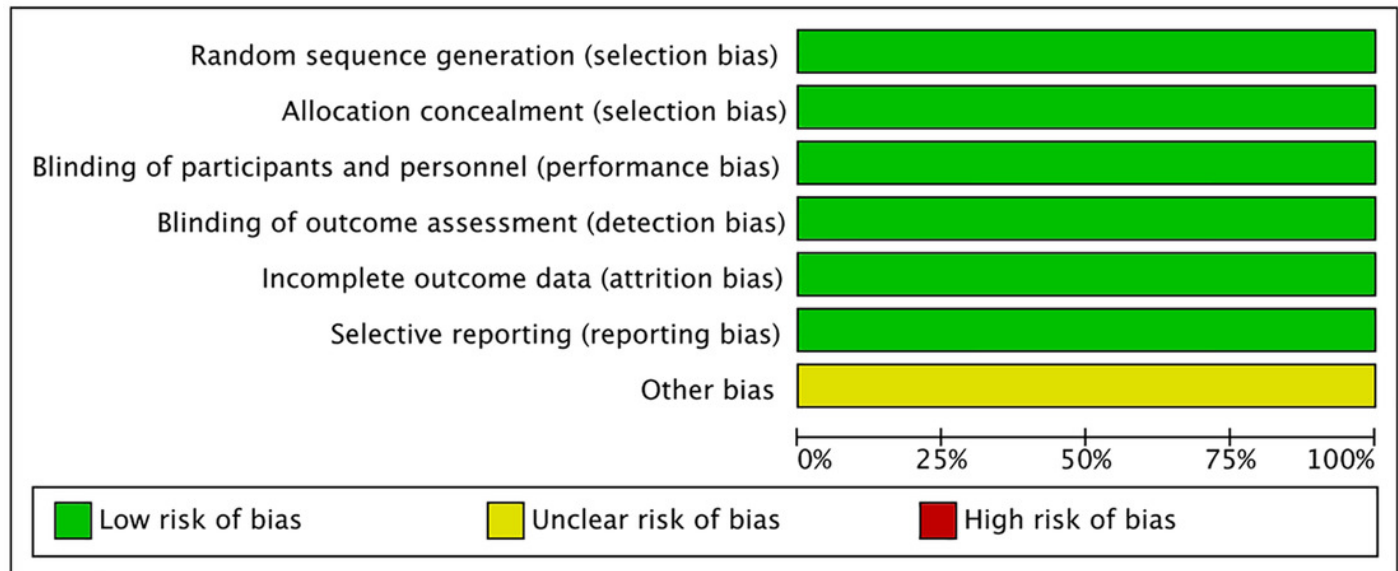



Figure 3

Risk of bias summary of all the retrieved studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Frank G. Holz2016	+	+	+	+	+	+	?
NCT01849692	+	+	+	+	+	+	?
NCT03386474	+	+	+	+	+	+	?
Pravin U. Dugel, MD2017	+	+	+	+	+	+	?
Pravin U. Dugel, MD2020	+	+	+	+	+	+	?
Y. Ogura 2021	+	+	+	+	+	+	?

Figure 4

Meta analysis for BCVA.

a

b

c

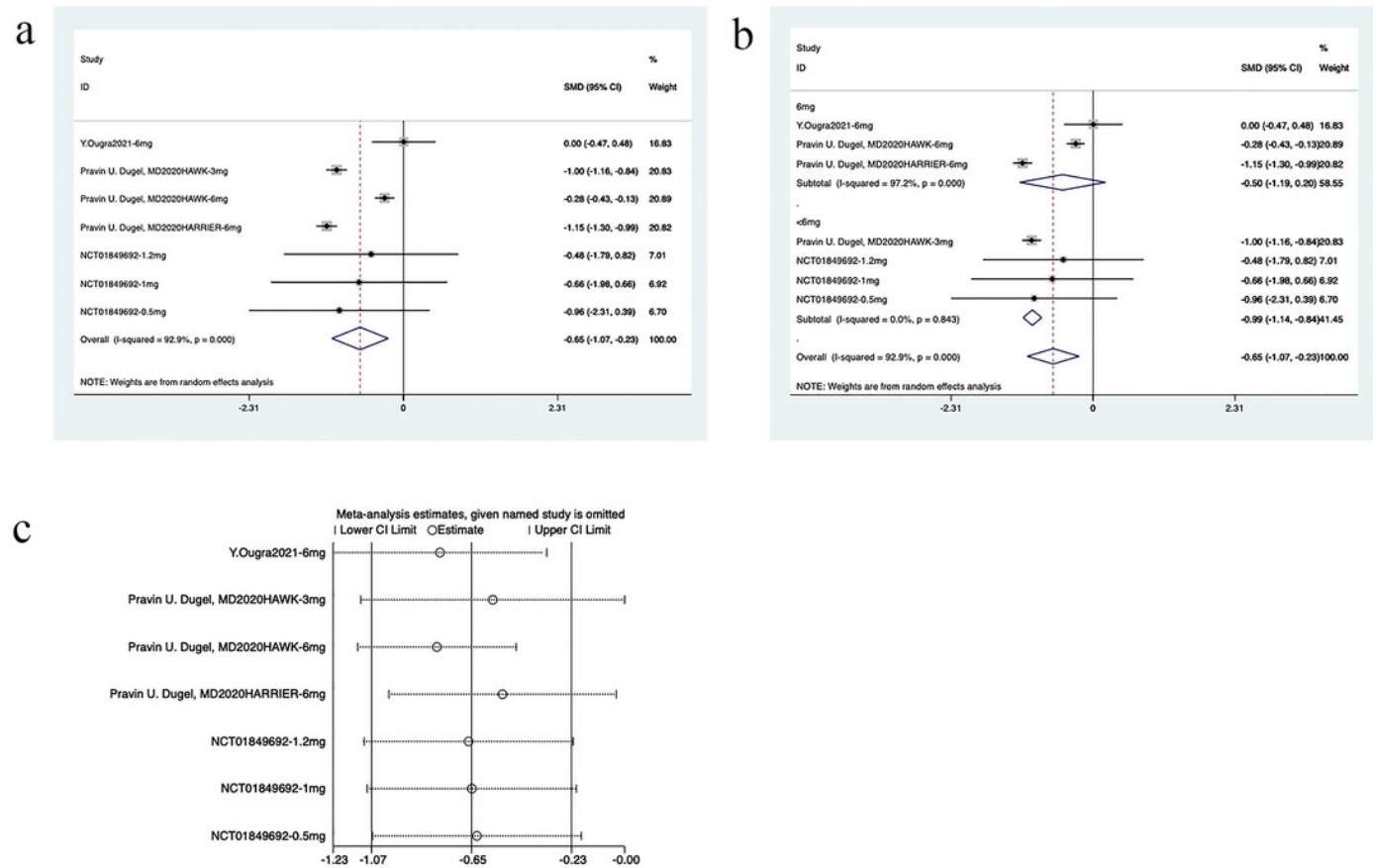



Figure 5

Meta analysis for CSFT.

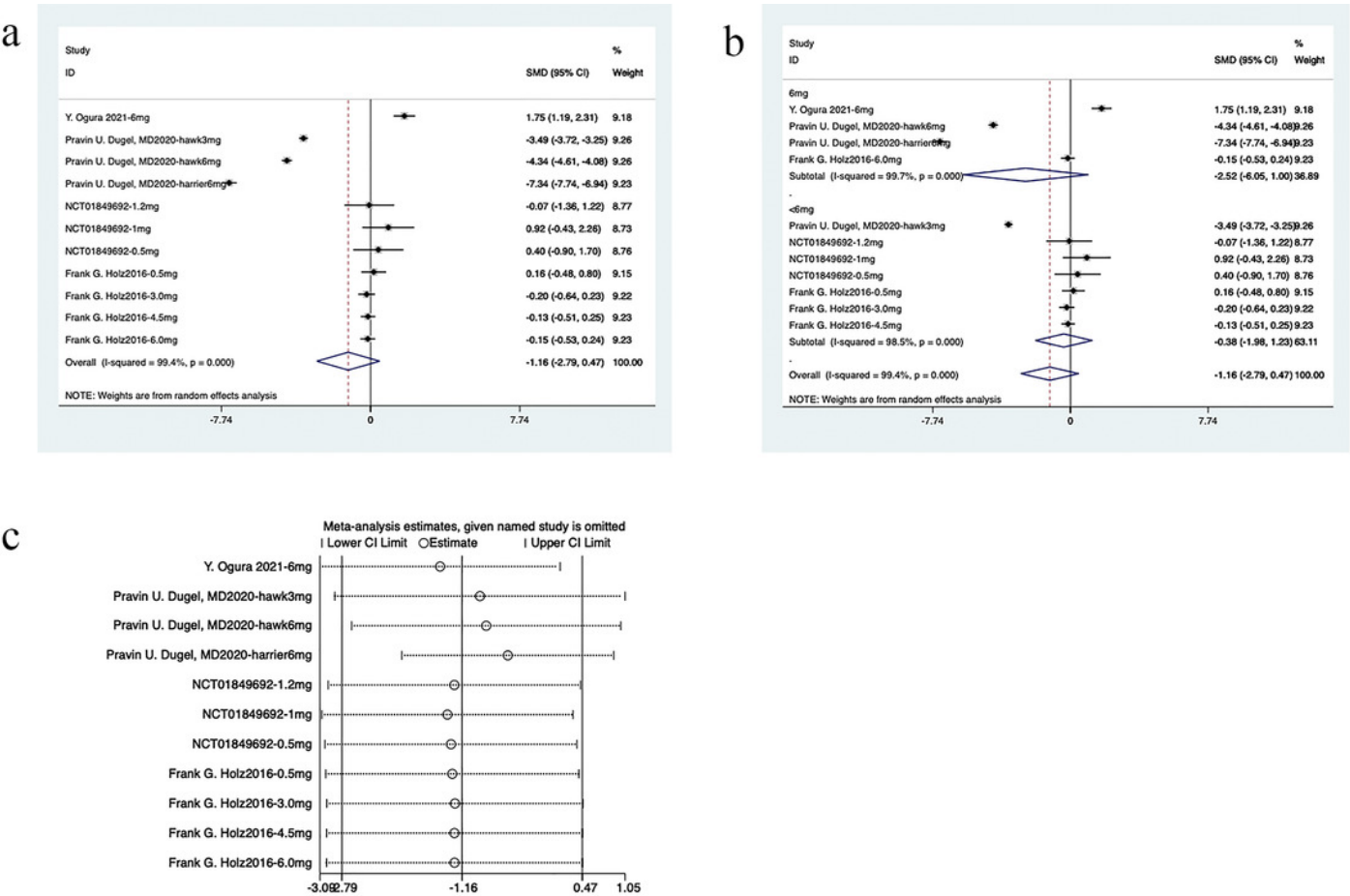



Figure 6

Meta analysis for Presence of IRF and/or SRF (F3).

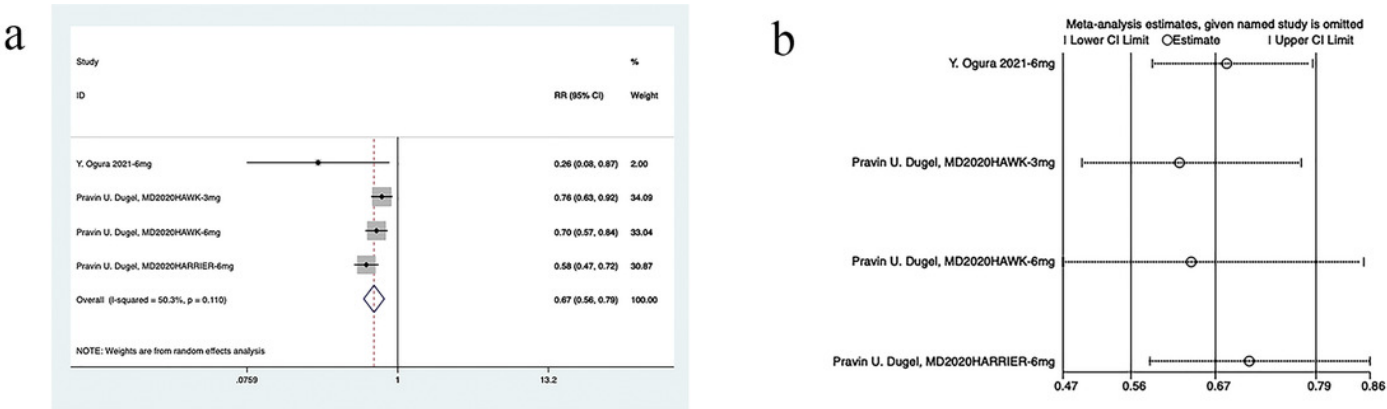
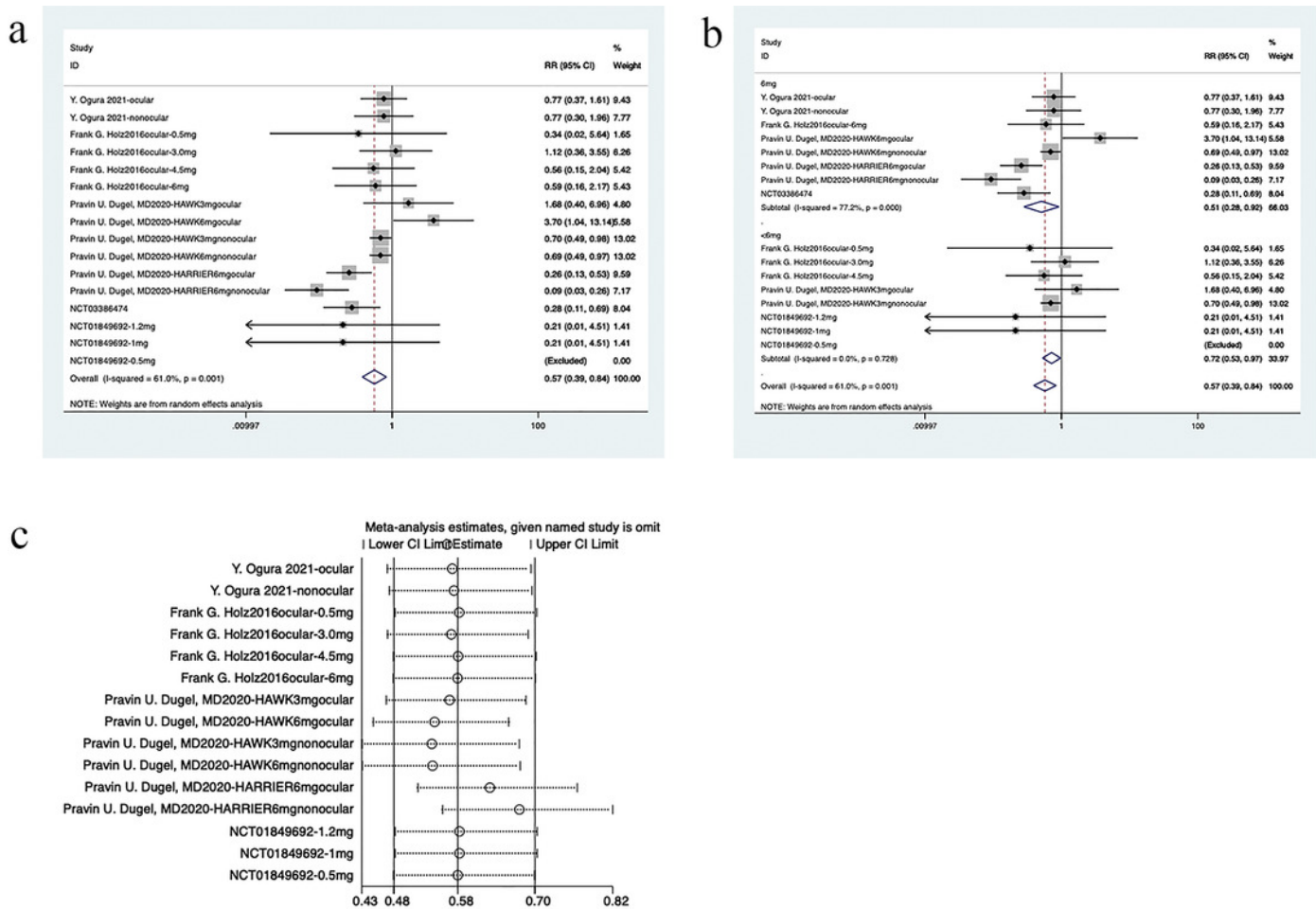



Figure 7

Sensitivity analysis.

Basic information of the included studies

1   **Table 1.** Basic information of the included studies

study	Experiment design	Country	Sample size(male)		Mean age(years)		Intervention		Follow up time	Outcome indicators
			EG	CG	EG	CG	EG	CG		
Y. Ogura 2021	RCT	Japan	39	30			Brolucizumab 6.0mg	Aflibercept 2.0mg	48weeks	F1 F2 F3
Frank G. Holz2016	RCT	United States, Europe, Israel, and Australia	11(5)	61(28)	75.7(6.5)	77.8(8.1)	RTH258 0.5mg	Ranibizumb 0.5mg	24weeks	F5 F6
			31(19)		78.4(8.3)		RTH258 3.0mg			
			47(21)		75.3(7.7)		RTH258 4.5mg			
			44(15)		74.8(9.8)		RTH258 6.0mg			
Pravin U. Dugel, MD 2017	RCT	United States	44(16)	45(20)	77.8	78.3	Brolucizumab 6.0mg	Aflibercept 2.0mg	56weeks	F5
Pravin U. Dugel, MD 2020	RCT	Argentina, Australia, Canada, Colombia, Israel, Japan, Mexico, New Zealand, Panama, Puerto Rico, and USA.	358(148)	360(166)	76.7(8.28)	76.2(8.8)	Brolucizumab 3 mg	Aflibercept 2 mg (HAWK)	48weeks	F1 F2 F3 F4 F5
			360(155)		76.7(8.95)		Brolucizumab 6 mg			
		Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, South Korea, Latvia,	370(160)	369(157)	74.8(8.58)	75.5(7.87)	Brolucizumab 6 mg	Aflibercept 2 mg (HARRIER)	48weeks	F1 F2 F3 F5 F6

NCT	Type	Country					EG	CG	Duration	Outcomes
		Lithuania, Netherlands,Norway, Poland, Portugal, Russia, Singapore,Slovakia, Spain, Switzerland,Taiwan, Turkey, UK,and Vietnam								
NCT03386474	nRCT	United States	107(38)	43(21)	80.6(8.63)	77.9(9.20)	Brolucizumab 6 mg	Aflibercept 2 mg	24weeks	F5
NCT01849692			10(7)	3(2)	77.5(3.6)	78.3(7.2)	ESBA1008 1.2mg	Ranibizumb 0.5mg(stage1)	56days	F1 F2
	RCT	US, Australia,the Dominican Republic	10(4)	3(1)	73.6(8.9)	82.0(3.6)	ESBA1008 1.0mg	Ranibizumb 0.5mg(stage1)		F1 F2 F5
			10(5)	3(1)	76.5(9.7)	81.7(11.0)	ESBA1008 0.6mg	Ranibizumb 0.5mg(stage2)		F1 F2 F5
			10(6)	3(2)	81.6(6.1)	76.7(3.8)	ESBA1008 0.5mg	Ranibizumb 0.5mg(stage2)		F1 F2 F5

2 RCT: randomized controlled trial EG: the experimental group CG: the control group

3 F1: BCVA(best-corrected visual acuity); F2:CSFT(central subfield thickness); F3:Presence of IRF and/or SRF, n (%); F4:Presence of

4 sub-RPE fluid, n (%); F5:safety1,Participants with ≥1 serious adverse event, n (%); F6: safety2,Participants with ≥1 adverse event,

5 n (%)