**Table 1a. Summary of included ranibizumab studies with follow-up of 12 months.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (date); name; NCT** | **Design** | **Patients (N)** | **Treatment arm** | **No. of injections per patient; mean (SD)** | **Treatment regimen:** monthly, PRN, TAE | **Baseline BVCA and CFT** | **Reference** |
| **RCTs** | | | | | | | |
| Berger (2015); NCT01135914 | Multicenter, open-label, parallel-group | N=75 patients | 0.5mg RAN | 9.2 (2.8) | Monthly | Baseline BVCA study eye, letters, mean (SD):  RAN 0.5mg: 63.1 (10.6)  CRT study eye, μm, mean (SD):  RAN 0.5mg: 448.5 (136.6) | [20] |
| Bressler (2016) | Post-hoc analysis, multicenter, | N=117 eyes (chronic persistent DME n=95) | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (58 to 71) | [21] |
| Bressler (2016) | Post-hoc analysis, multicenter | N=117 eyes (no persistent DME n=22) | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (56 to 71) | [21] |
| Brown (2013); RIDE (NCT00473382) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759) N=250 0.3mg RAN | 0.3 mg RAN | 10.6 (2.6) | Monthly | Baseline BCVA (letters), mean (SD):  RAN 0.3mg = 56.1 (12.2)  Baseline CFT, mean (SD), μM:  RAN 0.3mg = 478.6 (162.3) | [22] |
| Brown (2013); RISE (NCT00473330) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759)  N=252 0.5mg RAN | 0.5mg RAN | 10.9 (2.2) | Monthly | Baseline BCVA (letters), mean (SD):  RAN 0.5mg = 56.9 (11.6)  Baseline CFT, mean (SD), μM:  RAN 0.5mg = 463.8 (160.4) | [22] |
| Callanan (2017); NCT01492400 | open-label, parallel-group, multicenter | N= 182 RAN vs. N = 181 DEX implant | Intravitreal treatment with DEX implant  0.7 mg vs.  RAN 0.5 mg | 2.85 DEX implant vs. RAN 8.70 | Monthly | Mean BVCA in study eye, ETDRS letters (SD): RAN 0.5 mg = 60.4 (9.34)  Mean CRT in study eye, μm (SD): 471 (140) | [23] |
| Wells (2016a); NCT01627249 | Post-hoc, exploratory analysis | N=660; RAN CST ≥400μm: N=50 | 0.3 mg RAN | 9.7 (1.9) | PRN | Baseline BCVA (letters), mean (SD): 55.5 (10.5) | [26] |
| Wells (2016a); NCT01627249 | Post-hoc, exploratory analysis | N=660; RAN CST < 400μm: N=49 | 0.3-mg RAN IVR | 9.1 (2.3) | PRN | Baseline BCVA (letters), mean (SD): 57.7 (9.1) | [26] |
| Ishibashi (2015); (REVEAL); NCT00989989. | Double-blind, multicenter | N=369; RAN + sham laser (N = 133) | RAN 0.5 mg + sham laser | 7.8 (2.94) | Monthly | Baseline Mean BVCA ETDRS letters (SD):  58.8 (10.93);  Mean CRST, μm (SD):  419.2 (152.34); | [24] |
| Lafuente (2017); EudraCT trial number 2015-001082-74 | Single-blind controlled;  single center | N=33 subjects (42 eyes) | RAN 0.5mg | 6.5 (1.8) | Monthly for the first 4 months followed by PRN | BVCA at baseline, mean (SD):  30.88 (12.08)  CSMT at baseline, mean (SD), μm:  449.38 (100.67) | [25] |
| Massin (2010) (RESOLVE study); NCT00284050 | Double-blinded, sham-controlled, multicenter | N=102 (RAN arm); | RAN (0.3 mg, n=51 or 0.5 mg, n=51) | 10 (2.5) | Monthly (three monthly injections) | Baseline BVCA, mean (SD):  RAN pooled = 60.2 (9.9)  Baseline CRT, mean (SD), μm: RAN pooled = 455.4 (114.2) | [6] |
| Mitchell (2011) (RESTORE study); NCT00687804 | Double-blinded, Phase III study, multicenter | N=345; RAN 0.5mg N=116 | Intravitreal RAN (0.5 mg) injection + sham laser | 7.0 (2.81) | Monthly (for 3 months) then PRN | Mean BVCA ETDRS letters (SD):  RAN 0.5mg: 64.8 (10.11)  Mean CRT, μm (SD):  RAN 0.5mg: 426.6 (118.01) | [10] |
| Nepomuceno (2013); NCT01487629 | Prospective | N=45 (60 eyes; IVR = 28 eyes) | RAN 0.5 mg | 7.67 (0.60) | Monthly | Baseline BCVA, mean (SD):  RAN: 54 (0.06)  Baseline CST, mean (SD), μm: 421.9 (23.1) | [33] |
| Nguyen (2010); (READ-2); NCT00407381 | Prospective, Phase II, interventional, multicenter | N=126 (RAN 0.5 mg N=33 eyes) | 0.5 mg RAN | 9.3 | Monthly at baseline and month months 1,3, and 5, then PRN | Mean BVCA ETDRS letters:  RAN 0.5mg = 24.85  No CFT data | [34] |
| Payne (2017); (TREX-DME); NCT01934556 | Prospective, Phase I/II, multicenter,  controlled | N=150 eyes (116 patients); (TREX; 60 eyes) | IVR 0.3mg | 10.7 | Monthly | Baseline BCVA, mean ETDRS letters:  65.1  Baseline Mean CRT (μm):  434 | [36] |
| Payne (2017); (TREX-DME); NCT01934556 | Prospective, Phase I/II, multicenter,  controlled | N=150 eyes (116 patients); (Monthly 30 eyes) | IVR 0.3 mg | 13.1 | TAE | Baseline BCVA, mean ETDRS letters:  64.1  Baseline Mean CRT (μm):  475 | [36] |
| Pearce (2015); (RELIGHT); NCT01257815 | Prospective, open-label, single-arm, phase III, multicenter | N=109 (n=100 completed 12 months) | RAN 0.5 mg IVR | 6.8 | RAN 0.5mg monthly, then PRN | Baseline Mean BCVA (SD), ETDRS letters, n (%):  62.9 (11.4)  Baseline Mean CRT (SD), μm:  418.1 (159.2); n=102 | [37] |
| Prunte (2016); (RETAIN); NCT01171976 | Phase IIIb, single-masked, controlled, three-arm parallel-  group, multicenter | N=372 (TAE, n=128) | RAN 0.5 mg | 7.0 | TAE | Baseline Mean BCVA (SD), ETDRS letters, n (%):  63.9 (10.8)  Baseline Mean CSFT (SD), μm:  452.4 (131.2) | [13] |
| Tan (2014); ANZCTR; registration  number ACTRN12607000262404 | Prospective, blinded,  placebo-controlled, multicenter | N=36 (n=14 RAN patients completing the 12-month study) | IVR 0.5 mg | 8.0 | 6-monthly  injections of 0.5 mg RAN and thereafter monthly  PRN | BCVA, ETDRS letters, mean (SD):  RAN 39.5 (21.2)  Baseline Mean CFT, μm (SD):  RAN 615.6 (270.1) | [39] |
| **Real-world studies** | | | | | | | |
| Blinder (2017); (ECHO Study Report 1); NCT01918371 | Retrospective, open-label chart review; multicenter | Patients who received ≥3 intravitreal injections of anti-VEGF for the treatment of DME or macular edema secondary to RVO;  N=156; RAN = 89 | NR | 5.8 | Various; for the first 12 injections, mean time to next injection ranged from 1.2 to 1.7 months | BCVA, ETDRS letters, mean (SD):  56 (15.3)  Baseline Mean CRT, μm (SD):  413 (105) | [27] |
| Chatziralli (2017) | Retrospective, observational study | N = 322 (332 DME eyes) | 0.5mg RAN | 8.0 | Monthly (3 x IVR) then PRN | BCVA, ETDRS letters, mean (SD):  11.8 (3.5)  Baseline Mean CRT, μm (SD):  468 (113) | [28] |
| Egan (2017); (UK DR-EMR Users Group, Report 1) | Prospective, database, multicenter | Group 1 eyes were  treatment naïve at baseline for any treatment for DME  N= 3103 eyes | NR | 3.3 | various | BCVA, ETDRS letters, mean (SD):  51.1 (19.3)  Baseline Mean CFT, μm (SD):  468.4 (113.3) | [29] |
| Ghanchi (2016); (ADMOR) | Prospective, database; | N=41 (51 eyes); | IVR 0.5mg | 7 (2) | Initial monthly injections  for 3 months, then PRN | Baseline BCVA, ETDRS letters, mean (SD):  55.3 (13.4)  Baseline Mean CMT, μm (SD):  532 (129) | [30] |
| Giocanti-Aur´egan (NOT Hrarat) (2017) | Retrospective analysis, single center | N=78 (106 eyes); 39 eyes in the  SRD+ group | Various | 5.0 | 3 monthly injections  of RAN, followed by PRN (monthly) | Baseline BCVA, ETDRS letters, mean:  SRD+ = 45.2  Baseline Mean CRT, μm (SD):  SRD+ = 625 (130) | [31] |
| Giocanti-Aur´egan (NOT Hrarat) (2017) | Retrospective analysis, single center | N=78 (106 eyes); 39 eyes in the SRD- group; | Various | 6.0 | 3 monthly injections  of RAN, followed by PRN (monthly) | Baseline BCVA, ETDRS letters, mean:  SRD- = 45.3  Baseline Mean CRT, μm (SD):  SRD- = 480 (79) | [31] |
| Koç (2017) | Retrospective analysis of database records | N=101 eyes (RAN group | Group 1 = ranibizumab 0.5 mg | 3.1 (1.9) | Various; NR | **Baseline BCVA, ETDRS letters, mean (SD):**  49.8 (14.3)  **Baseline Mean CMT, μm (SD):**  460 (106.3) | [32] |
| Patrao (2016) | Retrospective, interventional case series, single center | N= 164 patients (200 eyes); | IVR 0.5 mg | 7.2 (2.3) | 3 consecutive monthly injections, followed by PRN | Baseline BCVA, ETDRS letters, mean (SD):  54.4 (15.26)  Baseline Mean CST, μm (SD):  490.16 (116.54) | [35] |
| Sato (2017); UMIN-CTR (UMIN000007649) | Retrospective case series, single center | N= 25 eyes RAN group | Ranibizumab (.5 mg/.05mL) | 4.1 (1.9) | Monthly | Baseline BCVA, mean (SD):  72 (15.26)  Baseline Mean CST, μm (SD):  490.16 (116.54) | [38] |
| Wong (2017) | Prospective analysis | N= 77 patients (104 eyes); | NR | 6.75 (1.51) | 4 monthly IVR injections, plus 2  If edema had not resolved | Baseline BCVA (letters), mean (SD):  61.6 (15.6)  Baseline Mean CRT, μm (SD):  471.8 (113.1) | [45] |
| Xu (2017) | Retrospective analysis, single center | N= 32 patients and 36 eyes (RAN group) | 0.5 mg ranibizumab | 7.2 (1.0) | 3 monthly injections then PRN | Baseline BCVA (letters), mean (SD):  RAN = 46.6 (10.9)  Baseline Mean CRT, μm (SD):  RAN = 473.9 (100.6) | [46] |

IVR: intravitreal RAN; RAN: ranibizumab; CST: central subfield thickness; CFT: central foveal thickness; CRT: central retinal thickness; CRST: central retinal subfield thickness; VEGF: Vascular endothelial growth factor; PRN: pro re nata/ as needed; SD: standard deviation; DME: diabetic macular edema; ETDRS: Early Treatment Diabetic Retinopathy Study; NR: not reported; EudraCT: European Clinical Trials Database; BCVA: best-corrected visual acuity; TREX: TReat and EXtend without macular laser photocoagulation; UK DR-EMR: United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group; UMIN-CTR: University Hospital Medical Information Network Clinical Trials Registry; NCT: ClinicalTrials.gov identifier.

**Table 1b. Summary of included ranibizumab studies with follow-up of 24 months.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author (date); name; NCT | **Design** | **Patients (N)** | **Treatment Arm** | **No. injections per patient; mean (SD)** | **Treatment regimen:** monthly, PRN, TAE | **Baseline BVCA and CFT** | **Reference** |
|  | **RCTs** | | | | | | |
| Bressler (2016) | Post-hoc analysis, multicenter, | N=117 eyes (chronic persistent DME n=61) | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (58 to 71) | [21] |
| Bressler (2016) | Post-hoc analysis, multicenter, | N=117 eyes (no persistent DME n=48) | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (56 to 71) | [21] |
| Jampol (2016) | Post-hoc analyses from DRCR.net randomized trial, multicenter | N=660; Base letter < 69 for RAN group = N=97 | RAN (0.3-mg) | BVCA 20/50 or Worse (Letter Score <69) = 15.9 (4.7) | Monthly | NR | [41] |
| Lafuente (2017); EudraCT trial number 2015-001082-74 | Single-blind controlled;  single center | N=33 subjects (42 eyes) | RAN 0.5mg | 8 (4) | Monthly for the first 4 months followed by PRN | BVCA at baseline, mean (SD):  30.88 (12.08)  CSMT at baseline, mean (SD), μm:  449.38 (100.67) | [25] |
| Nguyen (2010); (READ-2); NCT00407381 | Prospective, Phase II, interventional, multicenter | N=126 (RAN 0.5 mg N=33 eyes) | 0.5 mg RAN | 9.3 | Monthly at baseline and month months 1,3, and 5, then PRN | Mean BVCA ETDRS letters:  RAN 0.5mg = 24.85  No CFT data | [34] |
| Prunte (2016); (RETAIN); NCT01171976 | Phase IIIb, single-masked, controlled, three-arm parallel-  group, multicenter | N=372 (TAE, n=125) | RAN 0.5 mg TAE | 13 (3.7) | TAE | Baseline Mean BCVA (SD), ETDRS letters, n (%):  63.9 (10.8)  Baseline Mean CSFT (SD), μm:  452.4 (131.2) | [13] |
| Sepah (2016); (READ-3); NCT01077401 | Double-blinded, controlled, parallel study, multicenter | N=152 patients (eyes) DME; ran N= 59 eyes | IVR 0.5 mg | 18.4 | 6 monthly injections followed by PRN injections until month 24 | Baseline Mean BCVA, ETDRS letters, n:  RAN 0.5mg 26.30;  Baseline Mean CST, μm:  RAN 0.5mg 441.3.7 | [43] |
| Schmidt-Erfurth (2014); (RESTORE extension study); NCT00906464 | Phase IIIb, 12-month, randomized core study and 24-month open-label extension study, multicenter | Prior RAN N=83 | IVR 0.5 mg | 7.0 | Monthly | BVCA at baseline, mean (SD):  Prior RAN = 65.0 (10.11)  Baseline CRT, mean (SD), μm: Prior RAN = 426.6 (118.01) | [42] |
| Schmidt-Erfurth (2014); (RESTORE extension study); NCT00906464 | Phase IIIb, 12-month, randomized core study and 24-month open-label extension study, multicenter | Prior RAN + laser N=83 | IVR 0.5 mg | 6.0 | Monthly | BVCA at baseline, mean (SD):  Prior RAN+laser = 63.0 (9.99)  Baseline CRT, mean (SD), μm: Prior RAN+laser = 416.4 (119.91) | [42] |
| Singh (2016); (Analysis of RIDE and RISE); NCT00473382 and  NCT00473330, pooled | Exploratory, post- hoc analysis of 2 randomized, double-blinded, sham-injection controlled studies (RIDE and RISE) up to month 24; pooled data for RAN 0.3mg and 0.5mg groups, multicenter | N= 98 RAN participants only taking insulin | IVR 0.3 mg or 0.5 mg through month 24 | NR | Monthly | NR | [44] |
| Singh (2016); (Analysis of RIDE and RISE); NCT00473382 and  NCT00473330, pooled | Exploratory, post- hoc analysis of 2 randomized, double-blinded, sham-injection controlled studies (RIDE and RISE) up to month 24; pooled data for RAN 0.3mg and 0.5mg groups, multicenter | N= 124 RAN participants taking insulin and other medications | Sham injections  or IVR 0.3 mg or 0.5 mg through month 24 | NR | Monthly | NR | [44] |
| Singh (2016); (Analysis of RIDE and RISE); NCT00473382 and  NCT00473330, pooled | Exploratory, post- hoc analysis of 2 randomized, double-blinded, sham-injection controlled studies (RIDE and RISE) up to month 24; pooled data for RAN 0.3mg and 0.5mg groups, multicenter | N=185 RAN participants taking only non-insulin medications | Sham injections  or IVR 0.3 mg or 0.5 mg through month 24 | NR | Monthly | NR | [44] |
| Wells (2016b); **DRCR** study; NCT01627249 | Multicenter | N=660 (no. eyes analyzed at 24 months in RAN group: 192) | RAN (0.3 mg) | 14.8 (5.0) | Monthly | BCVA, ETDRS letters, mean (SD):  RAN BVCA 20/50 or worse (letter score <69) 56.1 (10.1)  Baseline Median CSF, μm (SD):  RAN 387 (122) | [12, 48] |
| Real-world studies | | | | | | | |
| Koç (2017) | Retrospective analysis of database records | N=101 eyes (RAN group | RAN 0.5 mg | 3.1 (1.9) | Various; NR | Baseline BCVA, ETDRS letters, mean (SD):  49.8 (14.3)  Baseline Mean CMT, μm (SD):  460 (106.3) | [32] |

IVR: intravitreal RAN; RAN: ranibizumab; CST: central subfield thickness; CFT: central foveal thickness; CSMT: central subfield macular thickness; PRN: pro re nata/ as needed; SD: standard deviation; DME: diabetic macular edema; ETDRS: Early Treatment Diabetic Retinopathy Study; NR: not reported; EudraCT: European Clinical Trials Database; BCVA: best-corrected visual acuity; NCT: ClinicalTrials.gov identifier.

**Table 1c. Summary of included ranibizumab studies with follow-up of 36 months.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author (date); name; NCT | **Design** | **Patients (N)** | **Treatment Arm** | **No. injections per patient; mean (SD)** | **Treatment regimen:** monthly, PRN, TAE | **Baseline BVCA and CFT** | **Reference** |
| **RCTs** | | | | | | | |
| Bressler (2016) | Post-hoc analysis, multicenter, | N=117 eyes (chronic persistent DME n=40) | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (58 to 71) | [21] |
| Bressler (2016) | Post-hoc analysis, multicenter, | N=117 eyes (no persistent DME n=60 | 0.5 mg RAN | 4 (2) | Monthly x4, then PRN | Baseline BCVA (letters), median (IQR):  65 (56 to 71) | [21] |
| Brown (2013); RIDE (NCT00473382) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759) N=125 0.3mg RAN | 0.3 mg RAN | 28 (11.2) | Monthly | NR | [22] |
| Brown (2013); RIDE (NCT00473382) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759) N=125 0.5 mg RAN | 0.5 mg RAN | 30 (9.2) | Monthly | NR | [22] |
| Brown (2013); RISE (NCT00473330) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759)  N=125 0.3mg RAN | 0.3mg RAN | 30 (10.2) | Monthly | NR | [22] |
| Brown (2013); RISE (NCT00473330) | Double-blinded, placebo-controlled, multicenter, Phase III | Adults with DME (n=759)  N=127 0.5mg RAN | 0.5mg RAN | 29 (10.4) | Monthly | NR | [22] |
| Elman (2015) | Multicenter | N= 235 DME; N=111 at 36 months | IVR 0.5mg | 17.0 | Monthly | BVCA at baseline, median:  RAN + deferred laser = 67.0  Baseline CST, median, μm: RAN + deferred laser = 394 | [47] |
| Schmidt-Erfurth (2014); (RESTORE extension study); NCT00906464 | Phase IIIb, 12-month, randomized core study and 24-month open-label extension study, multicenter | Prior RAN N=83 | IVR 0.5 mg | 7.0 | Monthly | BVCA at baseline, mean (SD):  Prior RAN = 65.0 (10.11)  Baseline CRT, mean (SD), μm: Prior RAN = 426.6 (118.01) | [42] |
| Schmidt-Erfurth (2014); (RESTORE extension study); NCT00906464 | Phase IIIb, 12-month, randomized core study and 24-month open-label extension study, multicenter | Prior RAN + laser N=83 | IVR 0.5 mg | 6.0 | Monthly | BVCA at baseline, mean (SD):  Prior RAN+laser = 63.0 (9.99)  Baseline CRT, mean (SD), μm: Prior RAN+laser = 416.4 (119.91) | [42] |

IVR: intravitreal RAN; RAN: ranibizumab; CST: central subfield thickness; CFT: central foveal thickness; CRT: central retinal thickness; PRN: pro re nata/ as needed; SD: standard deviation; DME: diabetic macular edema; NR: not reported; BCVA: best-corrected visual acuity; NCT: ClinicalTrials.gov identifier.