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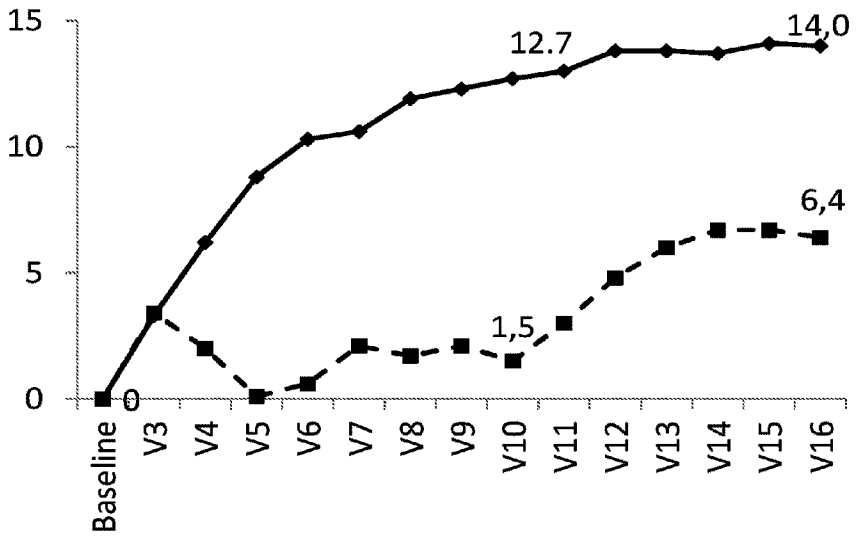

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Methods for treatment of wAMD with an active CNV lesion of less than 50% of the total lesion size and pharmaceutical compositions for the use therein are disclosed.

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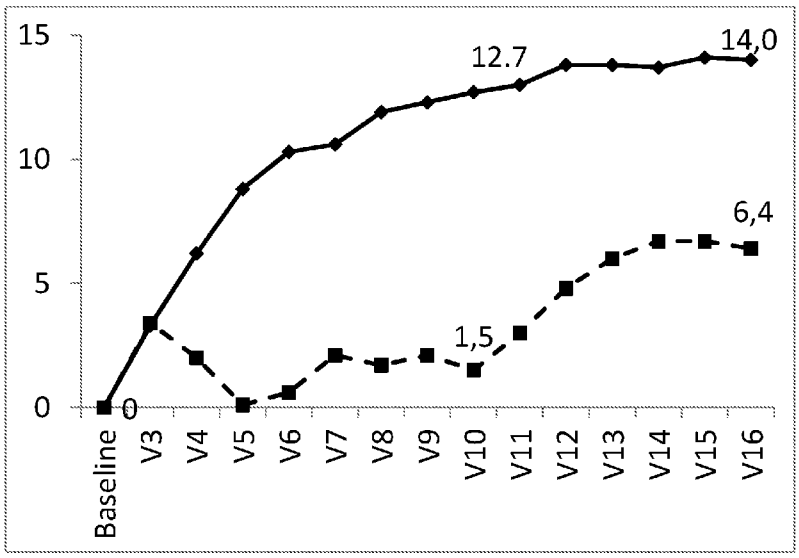
(54) **Title**: TREATMENT OF AGE RELATED MACULAR DEGENERATION WITH A SMALL ACTIVE CHOROIDAL NEOVASCULARIZATION LESION

Figure 1/2



(57) **Abstract**: Methods for treatment of wAMD with an active CNV lesion of less than 50% of the total lesion size and pharmaceutical compositions for the use therein are disclosed.

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USE OF ANTI-VEGF AGENTS TO TREAT LESIONS IN MACULAR DEGENERATION PATIENTS

Age related macular degeneration (AMD) is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. In the dry form, cellular debris called drusen accumulates between the retina and the choroid, and the retina can become detached. In the wet form (wAMD), which is more severe, blood vessels grow up from the choroid behind the retina which is also named choroidal neovascularization (CNV). As a result of CNV the retina can also become detached.

The proliferation of abnormal blood vessels in the retina is stimulated by vascular endothelial growth factor (VEGF). Antiangiogenics or anti-VEGF agents can cause regression of the abnormal blood vessels and improve vision when administered intravitreally. Several anti-VEGF drugs have been approved for use in the eye and are described in the following patent applications:

Aflibercept (Eylea®)	WO2000/75319
Bevacizumab (Avastin ®)	WO 9845331
Ranibizumab (Lucentis®)	WO9845331
Pegaptanib (Macugen®)	WO9818480
KH-902/conbercept (Langmu®)	WO2007112675

Besides anti-VEGF treatment wAMD can be also treated with photodynamic therapy with Verteporfin® (V®-PDT), whereby closure of leakage is induced by laser light in combination with visudyne, an i.v. injectable photosensitizer.

Clinical trials performed with anti-VEGF agents required the inclusion of patients with an active predominantly classic, subfoveal CNVarea that must occupy at least 50% of the total lesion [Rosenfeld et al. N Engl J Med 2006, 355:1419-1431; Brown et al. N Engl J Med 2006, 355:1432-1444; Heier et al. Ophthalmology 2012, 119:2537-2548; Regillo et al. Am J Ophthalmol 2008, 145:239-248]. Hence there is a dearth of information regarding the response of eyes with an active predominantly classic, subfoveal CNVarea that occupies less than 50% of the total lesion to anti-VEGF therapy.

The CATT research group compared the baseline characteristics, treatment frequency, visual acuity (VA), and morphologic outcomes of eyes with >50% of the lesion composed of blood (B50 group) versus all other eyes (Other group) enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). Treatment for the study eye was assigned randomly to either ranibizumab or bevacizumab and to 3 different dosing regimens over a 2-year period. Reading center graders evaluated baseline and follow-up morphology in color fundus photographs, fluorescein angiography

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(FA), and optical coherence tomography (OCT). Increases in mean visual acuity (VA) were similar in the "B50 group" and the "Other group" at 1 year (+9.3 vs +7.2 letters; P = 0.22) and at 2 years (9.0 vs 6.1 letters; P = 0.17). Mean lesion size in the "B50 group" decreased by 1.2 DA at both 1 and 2 years (primarily owing to resolution of hemorrhage) and increased in the "Other group" by 0.33 DA at 1 year and 0.91 DA at 2 years (P < 0.001). The authors concluded that the "B50 group" had a visual prognosis similar to the "Other group". Lesion size decreased markedly through 2 years. Eyes like those enrolled in CATT with neovascular AMD lesions composed of >50% blood can be managed similarly to those with less or no blood. [Altaweel MM et al. Ophthalmology. 2015 122(2):391-398].

However, the above evaluated subpopulation with >50% of the lesion composed of blood is not equal to the subpopulation of patients with active CNV lesion < 50% of the total lesion size of the study described in this application (example 1).

According to the invention there are two subtypes of wAMD: (I) small active CNV lesion – type of wAMD or (II) predominantly active CNV lesion – type of wAMD. The location of the lesion can be subfoveal or juxtafoveal affecting the fovea. The type of the lesion can be of all subtypes including predominantly classic, minimally classic, or occult.

The terminology for the two types of wAMD is preliminary. Alternate terms for the "small active CNV lesion – type of wAMD" may include:

1) "sCNV wAMD"
2) "wAMD with small active CNV"
3) "wAMD with reduced active CNV"
4) "wAMD with less CNV"
5) "Non-CNV related wAMD"
6) "wAMD Type 1"
7) "wAMD Type 2"
8) "wAMD Type X", where X is any number, letter or combination of both.

   In the under 1 – 8 listed alternative terms for "reduced active CNV – type of wAMD" alternative terms for "wAMD" can be:

   a. "wet AMD"
   b. "neovascular AMD"
   c. "nAMD"
   d. "exudative AMD"
   e. "eAMD"

Alternate terms for the "predominantly active CNV lesion – type of wAMD" may include:

1) "pCNV wAMD"
2) "wAMD with predominant active CNV"
3) "wAMD with active CNV"
4) "wAMD with large active CNV"
5) "CNV related wAMD"
6) "wAMD Type 1"
7) "wAMD Type 2"
8) "wAMD Type X", where X is any number, letter or combination of both.

In the under 1 – 8 listed alternative terms for "reduced active CNV – type of wAMD" alternative terms for "wAMD" can be

a. "wet AMD"
b. "neovascular AMD"
c. "nAMD"
d. "exudative AMD"
e. "eAMD"

In the following, the terms "sCNV wAMD" and "pCNV wAMD" will be used.

While the presence of active CNV lesion and thereby the diagnosis of wAMD is usually confirmed by fluorescence angiography (FA), the two wAMD types can be differentiated as follows:

1) "sCNV wAMD" is characterized by an active CNV lesion that occupies less than 50% of the total lesion size
2) "pCNV wAMD" is characterized by an active CNV lesion that occupies at least 50% of the total lesion size.

The location of the lesion can be subfoveal or juxtafoveal affecting the fovea. The type of the lesion can be of all subtypes including predominantly classic, minimally classic or occult.

The size of the active CNV lesion as well as the total lesion size is determined using Fluorescence Angiography (FA) as described in the MPS protocol [Macular Photocoagulation Study Group, Arch Ophthalmol 1991, 109:1242-1257].

With the invention, it is shown that lesions with small active portion of the CNV lesion (< 50% of total lesion size; "sCNV wAMD") respond well to treatment with anti-VEGF treatment, namely aflibercept, or PDT. This conclusion is based on an observation made in a clinical trial with patients with "sCNV wAMD" and "pCNV wAMD" which were treated either with intravitreal injection of aflibercept or V®-PDT. Surprisingly, the response determined by visual acuity of the "sCNV wAMD" patients to the aflibercept treatment was numerically higher to the response of the "pCNV wAMD" patients. This

was not expected because it is assumed that lesions with a large active portion of the CNV lesion are more receptive to the anti-leakage effect of the anti-VEGF treatment than lesions with small active portion of the CNV lesion. In addition, the response to the V®-PDT treatment of the "sCNV wAMD" patients is numerically higher to the response of the "pCNV wAMD" patients, which was not expected as well.

According to the invention, treatments for wAMD can be also used for the treatment of patients with "sCNV wAMD". Such treatment of patients with "sCNV wAMD" may be as follows:

1) Intravitreal anti-VEGF monotherapy similar to the treatment of wAMD, whereas anti-VEGF therapy refers to all approved and non-approved treatments aiming to attenuate free VEGF in the eye. This includes particularly aflibercept, ranibizumab, bevacizumab, KH-902, and pegaptanib, but is not limited to these compounds. Anti-VEGF treatment may be applied according to the following treatment schedules:
    a. Three monthly intravitreal injections or three intravitreal injections each 4 weeks apart followed by dosing every other month or every 4 weeks with or without the option to extend the treatment interval further during the later treatment phase.
    b. Treatment until visual acuity and/or retinal morphology (e.g. as assessed by OCT, Fluoresceine Angiography, Indocyanine Angiography, Funduscopy, etc.) stabilizes, followed by discontinuation of treatment. Re-initiation of treatment upon deterioration of visual acuity and/or retinal morphology.
    c. Any as needed (pro-re-nata – "PRN") regimen
    d. Any Treat&Extend regimen
    e. Any other treatment regimen that is or has been used for treatment of wAMD
2) Therapy with one or more of the following treatments. If more than one treatment is used, they may be used at the same time or sequentially.
    a. Anti-VEGF treatment as described under 1)
    b. Single or repeated applications of photodynamic therapy with Visudyne® (V®-PDT)
    c. Single or repeated applications of steroids (all available local or systemic application routes) including slow-release or depot formulations (e.g. Ozurdex, triamcinolone, dexamethasone, Iluvien, etc.)
    d. Radiation therapy
    e. Thermal laser therapy including sub-threshold treatments
    f. Surgical therapy
    g. Pharmacological vitreolysis (e.g. with Jetria or other approved or non-approved drugs)
    h. Systemically or locally applied inhibitors of tyrosine kinases
    i. Systemically or locally applied inhibitors of the VEGF receptor

Example 1:

A total of 304 Chinese subjects with age-related neovascular or wet age-related macular degeneration were enrolled in a randomized, double-blind clinical study to assess the efficacy of intravitreal (IVT) administrated aflibercept compared with V®-PDT on the mean change in BCVA (Best corrected visual acuity) from baseline to Week 28. BCVA of the study eye was assessed according to the standard procedures developed for the ETDRS (Early Treatment Diabetic Retinopathy Study) adapted for Age Related Eye Disease Study (AREDS). The key inclusion criteria were as follows:

- Signed and dated written ICF.
- Men and women ≥50 years of age.
- Active predominantly classic, subfoveal choroidal neovascularization (CNV) lesions secondary to AMD, including juxtafoveal lesions that affect the fovea, as evidenced by fluorescein angiography (FA), in the study eye.

  and
- ETDRS best corrected visual acuity (BCVA) of 73 to 25 letters in the study eye (Snellen activity equivalent of 20/40 to 20/320 in the study eye).

The following key exclusion criteria applied for the study eye:

- Total lesion size is greater than 12 disc areas (30.5 mm^2, including blood, scars and neovascularization), as assessed by FA
- Sub-retinal hemorrhages that is ≥50% of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size. (If the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV.)
- Presence of CNV with an origin other than wAMD. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than wAMD. Particular attention should be made to exclude subjects with polypoidal choroidal vasculopathy (PCV).
- Presence of scar, fibrosis, or atrophy involving the center of the fovea that indicates substantial irreversible vision loss.
- Presence of retinal pigment epithelial tears or rips involving the macula.

Eligible patients were randomized 3:1 to receive aflibercept (VTE) 2Q8 or V®-PDT (228 VTE+76 PDT). 194 patients with active CNV lesions >= 50% (147 VTE2Q8 + 47 PDT) and 106 patients with active CNV lesions < 50% (78 VTE2Q8 + 28 PDT) were included. The lesion size was determined by a central reading center based on the MPS protocol [Macular Photocoagulation Study Group, Arch Ophthalmol 1991, 109:1242-1257]. The active CNV size, the area of CNV (mm^2) as well as the total lesion size was measured using the FA. The central retinal thickness was determined by optical coherence tomography. In the VTE2Q8 group patients were treated with 2 mg (0.05 mL) aflibercept

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administered intravitreally at baseline, week 4, 8, 16, 24, 32, 40 and 48. In the PDT group V®-PDT was performed at baseline and potential PDT retreatment according to the guidelines for the use of PDT treatment in wAMD [Verteporfin Roundtable Participants, Retina. 2005; 25(2):119-34] were performed at week 12 and 24. At Week 28, after assessment of the primary and secondary endpoints, subjects in the PDT→VEGF Trap-Eye group received an IVT injection of 2.0 mg VEGF Trap-Eye, followed by additional 2.0 mg VEGF Trap-Eye injections at Weeks 32, 36, 40, and 48.

Intravitreal injections of 2 mg aflibercept was superior to V®-PDT with a mean change from baseline BCVA letter score at week 28 of 14.0 (-29 to 59) VTE2Q8 group versus 3.9 (-36 to 43) PDT group (P<0.0001) in the whole study population irrespective of the active CNV lesion size. Intravitreal injection of 2 mg aflibercept provided an effective treatment for patients with an active CNV lesion < 50% of total lesion size (mean change of BCVA from baseline at week 28: 16.7 (-21 to 59) see figure 2/2) which was comparable to the treatment outcome of patients with an active CNV lesion >= 50% of total lesion size (mean change of BCVA from baseline at week 28:12.7 (-29 to 40) see figure 1/2). V®-PDT treatment effect is numerically higher in patients with an active CNV lesion < 50% of total lesion size (mean change of BCVA from baseline at week 28: 8.0 (-18 to 43), see figure 2/2) than in patients with an active CNV lesion >= 50% of total lesion size (mean change of BCVA from baseline at week 28: 1.5 (-36 to 27) see figure 1/2).

In general, for most of the other efficacy parameters a more favorable outcome in patients with an active CNV lesion <50% of the total lesion size compared to those with an active CNV lesion >=50% of the total lesion size was observed for patients both treated with VTE2Q8 and V®-PDT (table 1).

Table 1: Efficacy outcome for VTE2Q8 and V®-PDT in patients with active CNV lesion size <50% and >=50% of total lesion size at week 28

	VTE2Q8		V®-PDT	
Efficacy parameter (unit)	Active CNV lesion <50%*	Active CNV lesion >=50%*	Active CNV lesion <50%*	Active CNV lesion >=50%*
Mean change of BCVA (letters)	16.7	12.7	8.0	1.5
Proportion of patients who maintained vision (letter loss <15 letters) (%)	97.4	99.3	92.9	91.7
Proportion of patients who gained 5 or more letters (%)	85.9	77.6	50.0	41.7
Proportion of patients who gained 10 or more letters (%)	73.1	66.7	32.1	27.1
Proportion of patients who gained 15 or more letters (%)	57.7	45.6	25.0	12.5
Proportion of patients who lost 5 or	5.1	6.8	17.9	31.3

more letters (%)				
Proportion of patients who lost 10 or more letters (%)	3.8	2.7	14.3	18.8
Proportion of patients who lost 15 or more letters (%)	2.6	0.7	7.1	8.3
Mean change in central retinal thickness (um)	-180.6	-180.4	- 109.5	-91.6
Mean change in CNV lesion size (mm^2)	-0.688	-1.009	-0.286	-0.201

* Active CNV lesion of total lesion size

Table 2: Efficacy outcome for VTE2Q8 and V®-PDT in patients with active CNV lesion size <50% and >=50% of total lesion size at week 52

	VTE2Q8		V®-PDT	
Efficacy parameter (unit)	Active CNV lesion <50%*	Active CNV lesion >=50%*	Active CNV lesion <50%*	Active CNV lesion >=50%*
Mean change of BCVA (letters)	18.1	14.0	13.4	6.4
Proportion of patients who maintained vision (letter loss <15 letters) (%)	96.2	98.0	96.4	87.5
Proportion of patients who gained 5 or more letters (%)	88.5	78.9	67.9	60.4
Proportion of patients who gained 10 or more letters (%)	78.2	67.3	57.1	50.0
Proportion of patients who gained 15 or more letters (%)	69.2	53.1	46.4	39.6
Proportion of patients who lost 5 or more letters (%)	6.4	8.2	21.4	29.2
Proportion of patients who lost 10 or more letters (%)	3.8	4.1	10.7	16.7
Proportion of patients who lost 15 or more letters (%)	3.8	2.0	3.6	12.5
Mean change in central retinal thickness (um)	-185.5	-192.1	-176.0	-166.6
Mean change in CNV lesion size (mm^2)	-0.688	-1.173	-0.286	-1.213

* Active CNV lesion of total lesion size

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Description of the Figures:

Figure 1/2: Mean change from baseline in ETDRS BCVA letter score by visit in subjects with an active CNV lesion ≥ 50% of total lesion size at baseline. The mean change in BCVA score (no. of letters) as measured by ETDRS from baseline at week 1 (V3) week 4 (V4), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8), week 24 (V9), week 28 (V10), Week 32 (Visit 11), Week 36 (Visit 12), Week 40 (Visit 13), Week 44 (visit 14), Week 28 (Visit 15), Week 52 (Visit 16) is shown for the VTE2Q8 group (solid line with diamonds) and the PDT->VTE group (dashed line with squares). At week 28 (V10) the mean change in BCVA score from baseline is 12.7 for the VTE2Q8 group and 1.5 for the PDT->VTE group. At week 52, the mean change in BCVA score from baseline is 14.0 for the VTE2Q8 group and 6.4 for the PDT->VTE group.

Figure 2/2: Mean change from baseline in ETDRS BCVA letter score by visit in subjects with an active CNV lesions < 50% of total lesion size at baseline. The mean change in BCVA score (no. of letters) as measured by ETDRS from baseline at week 1 (V3) week 4 (V4), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8), week 24 (V9), week 28 (V10), Week 32 (Visit 11), Week 36 (Visit 12), Week 40 (Visit 13), Week 44 (visit 14), Week 28 (Visit 15), Week 52 (Visit 16) is shown for the VTE2Q8 group (solid line with diamonds) and the PD->VTET group (dashed line with squares). At week 28 (V10) the mean change in BCVA score from baseline is 16.7 for the VTE2Q8 group and 8.0 for the PDT->VTE group. At week 52 (V10) the mean change in BCVA score from baseline is 18.1 for the VTE2Q8 group and 13.4 for the PDT->VTE group.

Embodiments:

The invention is further described by the following embodiments:

1. A method for treating wet age-related macular degeneration (wAMD) in a patient, wherein it is first established that the active size of the CNV lesion is smaller than 50% of the total lesion size, and then the patient is treated according to usual wAMD treatment schemes.

2. The method of embodiment 1, wherein active size of the CNV lesion is smaller than 50% of the total lesion size, and the patient is treated with an anti-VEGF treatment.

3. The method of embodiment 2, wherein the initial anti-VEGF therapy comprises a single injection or two, three, four, five, six, or more injections of a pharmaceutical composition for anti-VEGF therapy, each 4, 8, 12, or more weeks apart.

4. The method of embodiment 2, wherein at least 3 doses of anti-VEGF therapy are administered every 4 weeks.

5. The method of embodiment 2, wherein evaluation of the treatment response is performed 4, 8,

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12, or more weeks after the preceding anti-VEGF therapy.

6. The method of embodiment 2, 3, 4, or 5, wherein the anti-VEGF treatment comprises administration of a compound selected from aflibercept, ranibizumab, bevacizumab, KH-902, and pegaptanip.

7. The method of embodiment 1, wherein active size of the CNV lesion is smaller than 50% of the total lesion size, and the patient is treated with PDT using a photosensitizer.

8. The method of embodiment 7, wherein the treatment comprises administration of verteporfin as photosensitizer.

9. A pharmaceutical composition for use in the treatment of sCNV wAMD, comprising an anti-VEGF agent.

10. The pharmaceutical composition of embodiment 9, comprising aflibercept, ranibizumab, bevacizumab, KH-902, or pegaptanip.

11. A pharmaceutical composition for the treatment of sCNV wAMD, comprising a photosensitizer agent.

12. The pharmaceutical composition of embodiment 11, comprising verteporfin as photosensitizer agent.

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CLAIMS

1. Use of an anti-VEGF agent in therapy for treatment of neovascular (wet) age-related macular degeneration (AMD) in a subject, wherein:

the subject has an AMD lesion,

active choroidal neovascularization (CNV) affects less than 50% of total area of the subject's lesion,

the anti-VEGF agent is aflibercept, and

the therapy for the subject comprises an intravitreal aflibercept therapy suitable for treating wet AMD patients with active CNV affecting more than 50% of total AMD lesion area.

2. The use according to claim 1, wherein the anti-VEGF agent is for intravitreal administration once or two, three, four, five, six, or more times, each 4, 8, 12, or more weeks apart.

3. The use according to claim 2, wherein the anti-VEGF agent is for intravitreal administration once or two, three, four, five, six, or more times, each 12 or more weeks apart, and wherein the subject was previously treated once or two, three, four, five, six, or more times, each 4 or 8 weeks apart.

4. The use according to claim 2, wherein the anti-VEGF agent is for intravitreal administration at least three times, each 4 weeks apart.

5. The use according to claim 4, wherein the anti-VEGF agent is for intravitreal administration three times, each 4 weeks apart, followed by every 4 weeks.

6. The use according to claim 4, wherein the anti-VEGF agent is for intravitreal administration three times, each 4 weeks apart, followed by every 8 weeks.

7. The use according to claim 4, wherein the anti-VEGF agent is for intravitreal administration three times, each 4 weeks apart, followed by every 12 weeks.

8. The use according to claim 4, wherein the anti-VEGF agent is for intravitreal administration fourteen times, each 4 weeks apart, followed by every 12 weeks.

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9. The use according to claim 4, wherein the anti-VEGF agent is for intravitreal administration every 4 weeks to week 52, followed by every 12 weeks.

10. The use according to any one of claims 1-9, wherein the active CNV's area is determinable using fluorescence angiography.

11. The use according to claim 10, wherein:

the fluorescence angiography is fluorescein angiography,

the fluorescein angiography is based on the Macular Photocoagulation Study (MPS) protocol, and

sub-retinal hemorrhage affects less than 50% of total area of the subject's lesion.

12. The use according to any one of claims 1-11, wherein the anti-VEGF agent is 2 mg of aflibercept for intravitreal injection.

13. The use according to any one of claims 1-12, wherein the subject's response to the treatment is evaluated after 4, 8, 12, or more weeks.

14. The use according to claim 13, wherein the subject's response to the treatment is evaluated after 52 weeks.

15. The use according to claim 13 or 14, wherein the subject's response to the treatment is evaluated using optical coherence tomography (OCT).

16. The use according to claim 13 or 14, wherein the subject's response to the treatment is an increase in visual acuity.

17. The use according to claim 16, wherein the visual acuity is best corrected visual acuity (BCVA).

18. The use according to claim 17, wherein the subject's response to the treatment, as determined by an increase in visual acuity, is numerically higher than responses of wet AMD patients with active CNV affecting more than 50% of total lesion area.

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19. The use according to any one of claims 1-18, wherein the anti-VEGF agent treats the total AMD lesion in the subject.

20. An anti-VEGF agent suitable for use in the treatment of neovascular (wet) age-related macular degeneration (AMD) in a patient with an AMD lesion, wherein active choroidal neovascularization affects less than 50% of the lesion's total area, and wherein the anti-VEGF agent is aflibercept.

21. The anti-VEGF agent according to claim 20, wherein the treatment comprises an intravitreal aflibercept therapy suitable for treating wet AMD in a subject with active choroidal neovascularization affecting more than 50% of total AMD lesion area.

22. The anti-VEGF agent according to claim 20 or 21, which is 2 mg of aflibercept for intravitreal injection.

23. The anti-VEGF agent according to any one of claims 20-22, which is for intravitreal injection once or two, three, four, five, six, or more times, each 4, 8, 12, or more weeks apart.

24. The anti-VEGF agent according to any one of claims 20-23, which is for intravitreal injection once or two, three, four, five, six, or more times, each 12 or more weeks apart, and wherein the patient was previously treated once or two, three, four, five, six, or more times, each 4 or 8 weeks apart.

25. The anti-VEGF agent according to any one of claims 20-23, which is for intravitreal injection at least three times, each 4 weeks apart.

26. The anti-VEGF agent according to claim 25, which is for intravitreal injection three times, each 4 weeks apart, followed by every 4 weeks.

27. The anti-VEGF agent according to claim 25, which is for intravitreal administration three times, each 4 weeks apart, followed by every 8 weeks.

28. The anti-VEGF agent according to claim 25, which is for intravitreal administration

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three times, each 4 weeks apart, followed by every 12 weeks.

29. The anti-VEGF agent according to claim 25, which is for intravitreal administration fourteen times, each 4 weeks apart, followed by every 12 weeks.

30. The anti-VEGF agent according to claim 25, which is for intravitreal administration every 4 weeks to week 52, followed by every 12 weeks.

31. The anti-VEGF agent according to any one of claims 20-30, wherein the patient's response to the treatment is evaluated after 52 weeks.

32. The anti-VEGF agent according to any one of claims 20-31, wherein the patient's response to the treatment is an increase in visual acuity.

33. The anti-VEGF agent according to claim 32, wherein the visual acuity is best corrected visual acuity (BCVA).

34. The anti-VEGF agent according to claim 33, wherein the patient's response to the treatment, as determined by an increase in visual acuity, is numerically higher than responses of wet AMD subjects with active choroidal neovascularization affecting more than 50% of total AMD lesion area.

35. The anti-VEGF agent according to any one of claims 20-34, which treats the total AMD lesion in the patient.

36. Use of an anti-VEGF agent in therapy to treat age-related macular degeneration (AMD) in a subject, wherein:

the AMD is a neovascular (wet) AMD (wAMD),

active choroidal neovascularization (CNV), as identified by fluorescence angiography, affects less than 50% of total lesion area in the subject, and

the anti-VEGF agent is aflibercept.

37. The use of claim 36, wherein the fluorescence angiography is fluorescein

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angiography, and wherein the fluorescein angiography is based on the Macular Photocoagulation Study (MPS) protocol.

38. The use of claim 36, wherein the subject has a more favourable prognosis compared to wAMD patients with active CNV affecting more than 50% of total lesion area.

39. The use of claim 38, wherein the more favourable prognosis is a larger increase in visual acuity in response to the therapy.

40. The use of claim 36, wherein the subject's response to the therapy, as determined by an increase in visual acuity, is numerically higher than responses of wAMD patients with active CNV affecting more than 50% of total lesion area.

41. The use of claim 40, wherein the visual acuity is best corrected visual acuity (BCVA).

42. The use of claim 41, wherein the increase in BCVA of the subject from baseline to week 28 of the therapy is at least 5.

43. The use of claim 42, wherein the increase in BCVA is at least 10.

44. The use of claim 43, wherein the increase in BCVA is at least 15.

45. The use of claim 42, wherein the increase in BCVA of the subject from baseline to week 28 of the therapy is at least 8.

46. The use of claim 45, wherein the increase in BCVA is at least 16.

47. The use of claim 41, wherein the increase in BCVA of the subject from baseline to week 52 of the anti-VEGF therapy is at least 13.

48. The use of claim 47, wherein the increase in BCVA is at least 16.

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49. The use of claim 48, wherein the increase in BCVA is at least 18.

50. The use of any one of claims 41-49, wherein the BCVA is assessed based on standard procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) adapted for the Age-Related Eye Disease Study (AREDS).

51. The use of any one of claims 36-50, wherein the therapy comprises an intravitreal aflibercept therapy suitable for treating wAMD in a patient with active CNV affecting more than 50% of total lesion area.

52. The use of claim 51, wherein the aflibercept therapy comprises intravitreal injections of aflibercept every other month or every 4 weeks.

53. The use of claim 51, wherein the aflibercept therapy comprises intravitreal injections of aflibercept every 4 weeks.

54. The use of claim 53, wherein the aflibercept therapy comprises intravitreal injections of aflibercept every 4 weeks to week 52, followed by every 12 weeks.

55. The use of claim 53, wherein the aflibercept therapy comprises three initial intravitreal injections of aflibercept, each 4 weeks apart.

56. The use of any one of claims 51-55, wherein the subject's response to the therapy is evaluated after 4, 8, 12, or more weeks.

57. The use of claim 56, wherein the subject's response to the therapy is evaluated after 52 weeks.

58. The use of any one of claims 52-57, wherein each intravitreal injection includes a 2 mg dose of aflibercept.

59. The use of any one of claims 36-58, wherein the anti-VEGF therapy further comprises a photodynamic-therapy (PDT) treatment.

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60. The use of claim 59, wherein the PDT treatment uses verteporfin as a photosensitizer.

61. The use of claim 59 or 60, wherein the PDT treatment is provided in combination with the anti-VEGF agent.

62. The use of claim 59 or 60, wherein the PDT treatment is provided prior to or subsequent to the anti-VEGF agent.

63. The use of any one of claims 36-62, wherein the anti-VEGF agent treats the total lesion in the subject.

64. Use of an anti-VEGF agent in therapy to improve visual acuity of a patient with age-related macular degeneration (AMD), wherein:

the AMD is a neovascular (wet) AMD (wAMD),

active choroidal neovascularization (CNV) affects less than 50% of total lesion area in the patient, and

the anti-VEGF agent is aflibercept.

65. The use of claim 64, wherein the therapy includes measurement of visual acuity of the patient at baseline and at week 12.

66. The use of claim 64, wherein the therapy includes measurement of visual acuity of the patient at baseline and at week 52.

67. The use of claim 64, wherein the therapy includes measurement of visual acuity of the patient at baseline, at week 28, and at week 52.

68. The use of claim 64, wherein the therapy includes measurement of visual acuity of the patient at baseline, at week 12, and at week 52.

69. The use of claim 64, wherein the therapy includes measurement of visual acuity of the patient at week 12 and at week 52.

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70. The use of any one of claims 64-69, wherein the therapy comprises an intravitreal anti-VEGF therapy suitable for treating wAMD in a subject with active CNV affecting more than 50% of total lesion area.

71. The use of any one of claims 64-70, wherein the therapy comprises three initial doses of the anti-VEGF agent, each 4 weeks apart.

72. The use of claim 71, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, each 8 weeks apart.

73. The use of claim 71, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, each 4 weeks apart.

74. The use of claim 71, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, each 4 weeks apart, followed by every 12 weeks.

75. The use of claim 71, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, every 4 weeks to week 52, followed by every 12 weeks.

76. The use of any one of claims 70-75, wherein the patient's response to the therapy is evaluated after 4, 8, 12, or more weeks.

77. The use of claim 76, wherein the patient's response to the therapy is evaluated after 52 weeks.

78. The use of any one of claims 64-77, wherein the visual acuity is best corrected visual acuity (BCVA).

79. The use of claim 67, wherein the visual acuity is best corrected visual acuity (BCVA), and wherein the BCVA increases by at least 5, at least 10, or at least 15 from baseline to week 28 of the therapy.

80. The use of claim 67, wherein the visual acuity is best corrected visual acuity

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(BCVA), and wherein the BCVA increases by at least 8 from baseline to week 28 of the therapy.

81. The use of claim 80, wherein the BCVA increases by at least 16 from baseline to week 28 of the therapy.

82. The use of any one of claims 66-68, wherein the visual acuity is best corrected visual acuity (BCVA), and wherein the BCVA increases by at least 13 from baseline to week 52 of the therapy.

83. The use of claim 82, wherein the BCVA increases by at least 16 from baseline to week 52 of the therapy.

84. The use of claim 83, wherein the BCVA increases by at least 18 from baseline to week 52 of the therapy.

85. The use of any one of claims 78-84, wherein the BCVA is measured in accordance with standard procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) adapted for the Age-Related Eye Disease Study (AREDS).

86. The use of any one of claims 64-85, wherein the anti-VEGF agent is 2 mg of aflibercept.

87. The use of any one of claims 64-86, wherein the anti-VEGF agent treats the total lesion in the patient.

88. Use of aflibercept for treating wet age-related macular degeneration in a patient in whom the size of active CNV area is smaller than 50% of total lesion size and sub-retinal hemorrhage is <50% of total lesion size.

89. Use of aflibercept for improving visual acuity in a patient with wet age-related macular degeneration in whom the size of active CNV area is smaller than 50% of total lesion size and sub-retinal hemorrhage is <50% of total lesion size.

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90. The use according to claim 88 or 89, wherein the aflibercept is for administration by intravitreal injection.

91. The use according to claim 90, wherein the aflibercept is for administration by intravitreal injection in a 2-mg dose.

92. The use according to any one of claims 88-91, wherein the size of the active CNV area or the total lesion size is determinable by fluorescence angiography.

93. The use according to any one of claims 88-92, wherein the aflibercept is for administration one, two, three, four, five, six, or more times, each 4, 8, 12, or more weeks apart.

94. The use according to claim 93, wherein the aflibercept is for administration once or two, three, four, five, six, or more times, each 12 or more weeks apart, and wherein the patient was previously treated once or two, three, four, five, six, or more times, each 4 or 8 weeks apart.

95. The use according to any one of claims 88-93, wherein the aflibercept is for administration at least three times, each 4 weeks apart.

96. The use according to any one of claims 88-93, wherein the aflibercept is for administration every 4 weeks.

97. The use according to any one of claims 88-93, wherein the aflibercept is for administration fourteen times, each 4 weeks apart, followed by every 12 weeks.

98. Use of aflibercept in the manufacture of a medicament for treating wet age-related macular degeneration in a population of patients in whom the size of active CNV area is smaller than 50% of total lesion size and sub-retinal hemorrhage is <50% of total lesion size.

99. Use of aflibercept in the manufacture of a medicament for improving visual acuity in patients with wet age-related macular degeneration in whom the size of active CNV area is smaller than 50% of total lesion size and sub-retinal hemorrhage is <50% of total lesion size.

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100. The use according to claim 98 or 99, wherein the aflibercept is for administration by intravitreal injection.

101. The use according to claim 100, wherein the aflibercept is for administration by intravitreal injection in a 2-mg dose.

102. The use according to any one of claims 98-101, wherein the size of the active CNV lesion or the total lesion size is determinable by fluorescence angiography.

103. The use according to any one of claims 98-102, wherein the aflibercept is for administration one, two, three, four, five, six, or more times, each 4, 8, 12, or more weeks apart.

104. The use according to any one of claims 98-102, wherein the aflibercept is for administration at least three times, each at least 4 weeks apart.

105. The use according to any one of claims 98-103, wherein the aflibercept is for administration every 4 weeks.

106. The use according to any one of claims 98-103, wherein the aflibercept is for administration fourteen times, each 4 weeks apart, followed by every 12 weeks.

107. An anti-VEGF agent suitable for use in the treatment of wet age-related macular degeneration (wAMD) in a patient in whom it is first established by fluorescence angiography that the size of the active CNV lesion is smaller than 50% of total lesion size, wherein the anti-VEGF agent is aflibercept.

108. The anti-VEGF agent for use in the treatment of wAMD according to claim 107, wherein the treatment comprises at least 3 injections of the anti-VEGF agent, each 4 weeks apart.

109. The anti-VEGF agent of claim 108, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

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110. The anti-VEGF agent of claim 108, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 8 weeks.

111. The anti-VEGF agent of claim 108, wherein the treatment comprises 14 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 12 weeks.

112. The anti-VEGF agent of any one of claims 107-111, which is 2 mg of aflibercept for intravitreal injection.

113. The anti-VEGF agent of any one of claims 107-112, wherein the patient's response to the treatment is evaluated after 4, 8, 12, or more weeks.

114. The anti-VEGF agent of claim 113, wherein the patient's response to the treatment is evaluated after 52 weeks.

115. The anti-VEGF agent of claim 113 or 114, wherein the patient's response to the treatment is evaluated using optical coherence tomography (OCT).

116. The anti-VEGF agent of any one of claims 107-115, which treats the total lesion in the patient.

117. An anti-VEGF agent suitable for use in the treatment of wet age-related macular degeneration (wAMD) in a patient in whom it is first established by fluorescence angiography that the size of active CNV lesion is smaller than 50% of total lesion size, wherein:

the anti-VEGF agent is aflibercept,

the fluorescence angiography is fluorescein angiography, and

<50% of the total lesion size is composed of blood.

118. The anti-VEGF of claim 117, wherein the treatment comprises at least 3 injections of the anti-VEGF agent, each 4 weeks apart.

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119. The anti-VEGF agent of claim 118, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

120. The anti-VEGF agent of claim 118, wherein the treatment comprises 14 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 12 weeks.

121. The anti-VEGF agent of claim 120, which is 2 mg of aflibercept for intravitreal injection.

122. The anti-VEGF agent of claim 121, wherein the patient's response to the treatment is evaluated after 52 weeks.

123. An anti-VEGF agent suitable for use in the treatment of wet age-related macular degeneration (wAMD) in a patient in whom it is first established by fluorescence angiography that the size of active CNV lesion is smaller than 50% of total lesion size, wherein:

the anti-VEGF agent is aflibercept,

the fluorescence angiography is fluorescein angiography,

sub-retinal hemorrhage is <50% of total lesion size, and

if blood is under the patient's fovea, the blood is less than one disc area in size.

124. The anti-VEGF agent of claim 123, wherein the treatment comprises at least 3 injections of the anti-VEGF agent, each 4 weeks apart.

125. The anti-VEGF agent of claim 124, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

126. An anti-VEGF agent suitable for use in the treatment of wet age-related macular degeneration (wAMD) in a patient in whom it is first established by fluorescence angiography that the size of active CNV lesion is smaller than 50% of total lesion size, wherein the anti-VEGF agent is aflibercept, the fluorescence angiography is fluorescein angiography, and the patient does not have:

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- a total lesion size that is greater than 12 disc areas, as assessed by fluorescein angiography;

- a sub-retinal hemorrhage that is ≥50% of the total lesion area;

- blood under the patient's fovea that is 1 or more disc areas in size;

- a CNV with an origin other than wAMD;

- a history or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than wAMD;

- presence of scar, fibrosis, or atrophy involving a center of the patient's fovea that is indicative of substantial irreversible vision loss; or

- presence of retinal pigment epithelial tears or rips involving the patient's macula.

127. The anti-VEGF agent of claim 126, wherein the treatment comprises at least 3 injections of the anti-VEGF agent, each 4 weeks apart.

128. The anti-VEGF agent of claim 127, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

129. Use of an anti-VEGF agent for treatment of wet age-related macular degeneration in a patient in whom the size of active CNV lesion is smaller than 50% of total lesion size, wherein the patient was selected for the treatment, and wherein the anti-VEGF agent is aflibercept.

130. Use of an anti-VEGF agent to improve visual acuity in a patient with wet age-related macular degeneration in whom the size of active CNV lesion is smaller than 50% of total lesion size, wherein the patient was selected for the treatment, and wherein the anti-VEGF agent is aflibercept.

131. The use of claim 129 or 130, wherein the anti-VEGF agent is for administration once or two, three, four, five, six, or more times, each 4, 8, 12, or more weeks apart.

132. The use of claim 131, wherein the anti-VEGF agent is for administration once or two, three, four, five, six, or more times, each 12 or more weeks apart, and wherein the patient was previously treated once or two, three, four, five, six, or more times, each 4 or 8 weeks apart.

133. The use of any one of claims 129-131, wherein the anti-VEGF agent is for

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administration at least three times, each 4 weeks apart.

134. The use of claim 133, wherein the anti-VEGF agent is for administration at least three times, each 4 weeks apart, followed by every 4 weeks.

135. The use of claim 133, wherein the anti-VEGF agent is for administration at least three times, each 4 weeks apart, followed by every 8 weeks.

136. The use of claim 133, wherein the anti-VEGF agent is for administration fourteen times, each 4 weeks apart, followed by every 12 weeks.

137. The use of any one of claims 133-136, wherein the anti-VEGF agent is 2 mg of aflibercept for intravitreal injection.

138. The use of any one of claims 133-137, wherein the patient's response to the treatment is evaluated after 4, 8, 12, or more weeks.

139. The use of claim 138, wherein the patient's response to the treatment is evaluated after 52 weeks.

140. The use of claim 139, wherein the patient's response to the treatment is evaluated using optical coherence tomography (OCT).

141. The use of any one of claims 129-140, wherein the anti-VEGF agent treats the total lesion in the patient.

142. Use of an anti-VEGF agent in the manufacture of a medicament for treating wet age-related macular degeneration or for improving visual acuity in patients with wet age-related macular degeneration, wherein the medicament is for administration to patients selected for treatment, wherein said selection is for patients in whom the size of active CNV lesion is smaller than 50% of total lesion size, and wherein the anti-VEGF agent is aflibercept.

143. Use of an anti-VEGF agent in therapy to improve visual acuity of a patient with wet

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age-related macular degeneration (wAMD) and a small active choroidal neovascularization (sCNV) lesion, wherein:

the sCNV lesion occupies less than 50% of total lesion area in the patient's eye;

the anti-VEGF agent is aflibercept; and

the anti-VEGF agent treats the total lesion.

144. The use of claim 143, wherein the therapy includes measurement of visual acuity of the patient at baseline and at week 12.

145. The use of claim 143, wherein the therapy includes measurement of visual acuity of the patient at baseline and at week 52.

146. The use of claim 143, wherein the therapy includes measurement of visual acuity of the patient at baseline, at week 28, and at week 52.

147. The use of claim 143, wherein the therapy includes measurement of visual acuity of the patient at baseline, at week 12, and at week 52.

148. The use of claim 143, wherein the therapy includes measurement of visual acuity of the patient at week 12 and at week 52.

149. The use of claim 143, wherein the therapy for the patient comprises an intravitreal anti-VEGF therapy suitable for treating wet age-related macular degeneration in a subject with a predominantly active choroidal neovascularization lesion that occupies more than 50% of total lesion area.

150. The use of claim 143, wherein the therapy comprises three initial doses of the anti-VEGF agent, each 4 weeks apart.

151. The use of claim 150, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, each 8 weeks apart.

152. The use of claim 150, wherein the therapy further comprises subsequent doses of the

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anti-VEGF agent, each 4 weeks apart.

153. The use of claim 152, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, every 4 weeks to week 52, followed by every 12 weeks.

154. The use of claim 150, wherein the therapy further comprises subsequent doses of the anti-VEGF agent, each 12 weeks apart.

155. The use of any one of claims 143-154, wherein the patient's response to the therapy is evaluated after 4, 8, 12, or more weeks.

156. The use of claim 155, wherein the patient's response to the therapy is evaluated after 52 weeks.

157. The use of any one of claims 143-156, wherein the visual acuity is best corrected visual acuity (BCVA).

158. The use of claim 146, wherein the visual acuity is best corrected visual acuity (BCVA), and wherein the BCVA increases by at least 5, at least 10, or at least 15 from baseline to week 28 of the therapy.

159. The use of claim 146, wherein the visual acuity is best corrected visual acuity (BCVA), and wherein the BCVA increases by at least 8 from baseline to week 28 of the therapy.

160. The use of claim 159, wherein the BCVA increases by at least 16 from baseline to week 28 of the therapy.

161. The use of any one of claims 145-147, wherein the visual acuity is best corrected visual acuity (BCVA), and wherein the BCVA increases by at least 13 from baseline to week 52 of the therapy.

162. The use of claim 161, wherein the BCVA increases by at least 16 from baseline to week 52 of the therapy.

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163. The use of claim 162, wherein the BCVA increases by at least 18 from baseline to week 52 of the therapy.

164. The use of any one of claims 157-163, wherein the BCVA is measured in accordance with standard procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) adapted for the Age-Related Eye Disease Study (AREDS).

165. The use of any one of claims 143-164, wherein the anti-VEGF agent is 2 mg of aflibercept for intravitreal administration.

166. Use of aflibercept for treatment of a lesion in an eye of a subject with wet age-related macular degeneration (wAMD), wherein:

active choroidal neovascularization (CNV) occupies less than 50% of the lesion's total size,

sub-retinal hemorrhage is less than 50% of the lesion's total size, and

the aflibercept treats the total lesion.

167. An anti-VEGF agent suitable for use in treatment of a lesion in a subject's eye in which active choroidal neovascularization (CNV), as identified by fluorescence angiography, occupies less than 50% of total lesion size, wherein:

the subject has wet age-related macular degeneration (wAMD),

the anti-VEGF agent treats the total lesion, and

the anti-VEGF agent is aflibercept.

168. The anti-VEGF agent of claim 167, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart.

169. The anti-VEGF agent of claim 168, wherein the treatment comprises 3 injections of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

170. The anti-VEGF agent of claim 168, wherein the treatment comprises 3 injections of a 2-mg dose of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 4 weeks.

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171. The anti-VEGF agent of claim 168, wherein the treatment comprises 3 injections of a 2-mg dose of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 8 weeks.

172. The anti-VEGF agent of claim 168, wherein the treatment comprises 14 injections of a 2-mg dose of the anti-VEGF agent, each 4 weeks apart, followed by consecutive injections of the anti-VEGF agent every 12 weeks.

173. The anti-VEGF agent of claim 168, wherein the treatment comprises an injection of the anti-VEGF agent every 4 weeks to week 52, followed by every 12 weeks.

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Figure 1/2

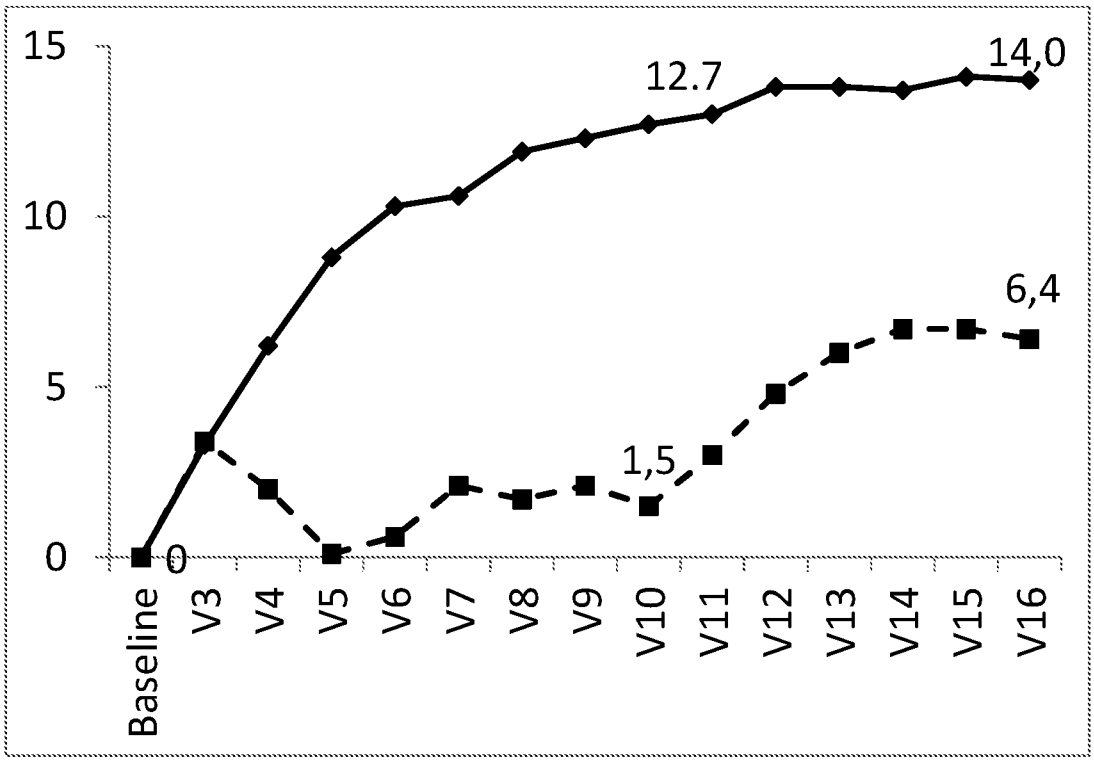
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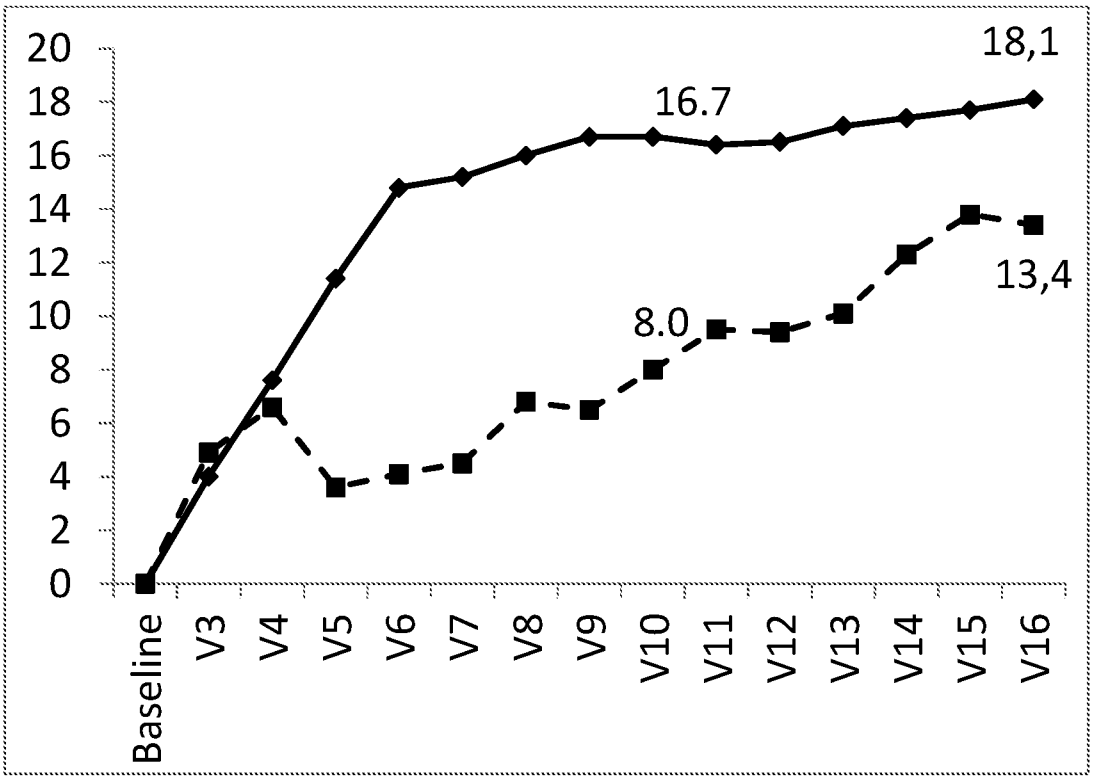
Figure 2/2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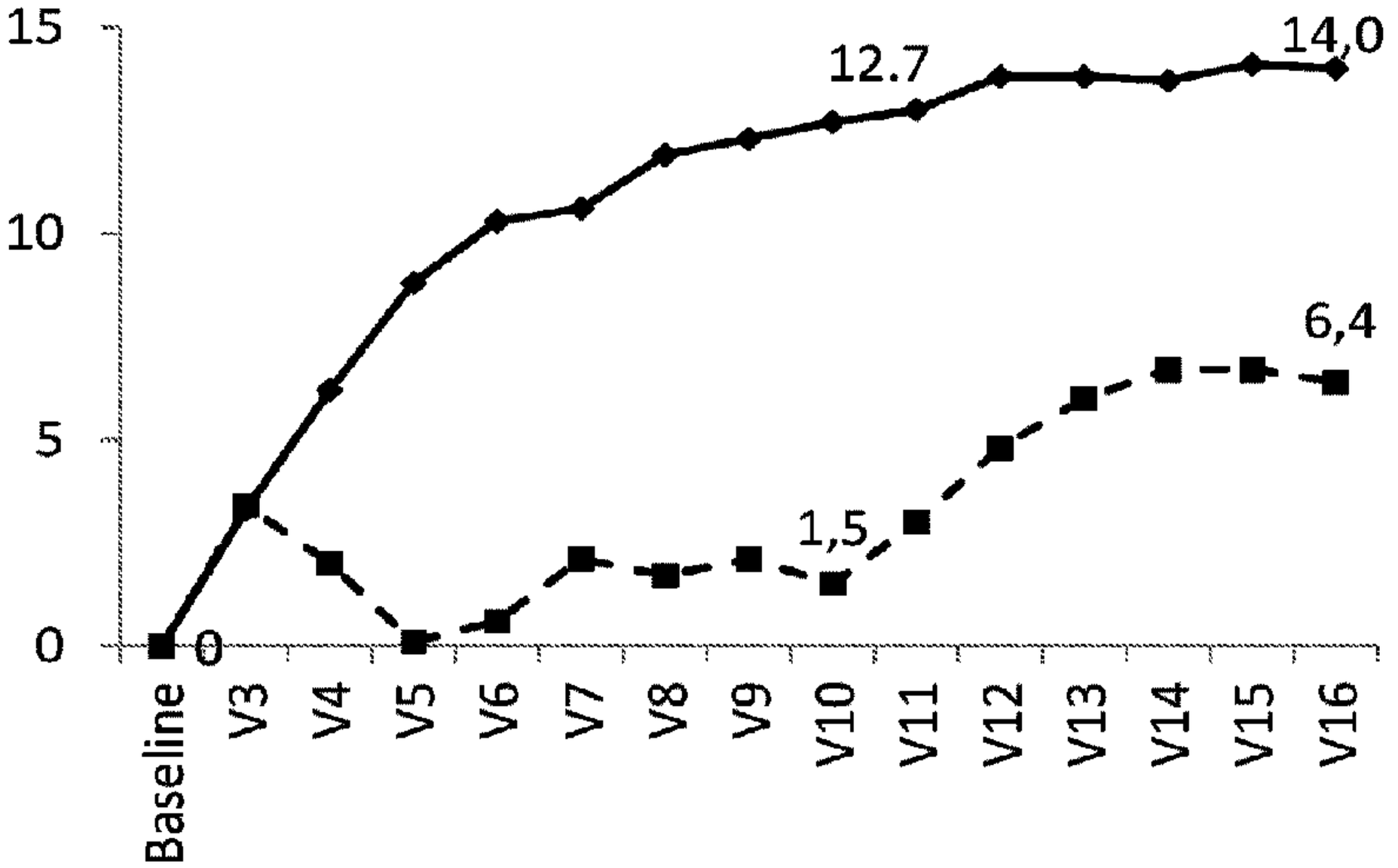
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