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DESCRIPTION

[0001] This disclosure is directed to synthetic retinal derivatives for use in improving visual function in a subject with an endogenous retinoid deficiency.

Background

[0002] Inherited retinal diseases (IRD) caused by gene mutations that disrupt or interfere with the production, conversion and/or regeneration of 11-cis-retinal result in severe visual impairment and childhood blindness. 11-cis-Retinal is an endogenous retinoid produced in and by the retinal pigment epithelium (RPE) from the isomerization and oxidation of the all-trans-retinol (Vitamin A derived from the diet). 11-cis-Retinal functions as a chromophore and covalently binds to the protein opsin to form isorhodopsin. Vision is initiated when a light photon is captured by 11-cis-retinal, resulting in the isomerization to all-trans-retinal and disassociation from opsin. Vision is sustained by the cycling of all-trans-retinal back into 11-cis-retinal, which occurs by a complex series of biochemical reactions involving multiple enzymes and proteins in the retinoid or visual cycle.

[0003] Endogenous retinoid deficiencies, such as those caused by mutations in the genes encoding the enzymes and proteins utilized in the visual cycle, impair the synthesis of 11-cis-retinal, the result of which leads to visual disorders due to the shortage or depletion of 11-cis-retinal.

[0004] For example, Retinitis Pigmentosa (RP) is an inherited retinal disease that features degeneration of rod and cone photoreceptor cells (Hartong, D.T. et al., Lancet, 368, 1795-1809 (2006)). There are a variety of forms of RP all of which show various limitations of visual performance over time and the course and progression of the disease show considerable variability between individuals. RP is typically characterized by initial symptoms of night blindness, with onset in adolescence or early adulthood, loss of peripheral vision and, as the disease progresses, loss of central vision that can lead to blindness or severe visual impairment. The age-at-onset of symptoms is highly variable and ranges from childhood to mid-adulthood. RP Disease Classification can be by made by age of onset, for example, congenital RP (sometimes referred to as LCA), juvenile onset RP, teenage onset RP, adult onset RP, and late onset RP. ERG responses are an early indicator of loss of rod and cone function in RP and diminution of ERG responses can be evident within the first few years of life, even though symptoms appear much later.

[0005] Typical RP presents as primary degeneration of rods, with secondary degeneration of cones, and is consequently described as a rod-cone dystrophy, with rods being more affected than cones. This sequence of photoreceptor involvement explains why some RP subjects initially present with night blindness, and only in later life become visually impaired in all light conditions. Alternatively, in about 10-20% of subjects with RP exhibit cone-rod dystrophy.

[0006] RP can be caused by defects in many different genes and their related disease pathways. At present, more than 200 causative RP mutations have been detected in more than 100 different genes.

[0007] RP genotypes are heterogeneous, and RP subjects with the same mutation can exhibit different phenotypes. RP may be classified by inheritance type, for example, autosomal dominant (ad) RP, autosomal recessive (ar) RP, X-linked (XL) or sex-linked recessive RP, sporadic RP (simplex RP; most are recessive), or Digenic RP.. RP is currently estimated to affect at least 300,000 individuals worldwide, of which approximately 20%-30% are autosomal recessive (arRP).

[0008] In recent years, mutations in the *LRAT* and *RPE65* genes have been discovered in RP subjects with arRP or adRP. These specific mutations, as well as mutations in ABCA4 and RDH12 are linked to defects in retinoid metabolism of the visual cycle and may result in photoreceptor degeneration. Endogenous retinoid deficiencies, such as those caused by mutations in the genes encoding the enzymes and proteins utilized in the visual cycle impair the synthesis of 11-cis-retinal, the result of which leads to visual disorders due to the shortage or depletion of 11-cis-retinal.

[0009] The protein encoded by the RPE65 gene has a biochemical association with retinol binding protein and 11-cis-retinol dehydrogenase and is essential for 11-cis-retinal production (Gollapalli, D.R. et al., Biochemistry. 42(19):5809-5818 (2003) and Redmond, T.M. et al., Nat Genet. 20(4):344-351 (1998)). 11-Cis-retinal is an endogenous retinoid produced in and by the retinal pigment epithelium (RPE) from the isomerization and oxidation of the all-trans-retinol (Vitamin A derived from the diet). 11-Cis-retinal functions as a chromophore and covalently binds to the protein opsin to form rhodopsin. Vision is initiated when a light photon is captured by 11-cis-retinal, resulting in the isomerization to all-trans-retinal and disassociation from opsin. Vision is sustained by the cycling of all-trans-retinal back into 11-cis-retinal, which occurs by a complex series of biochemical reactions involving multiple enzymes and proteins in the retinoid or visual cycle. Preclinical and clinical information show that loss of the function of the RPE65 protein blocks retinoid processing after esterification of vitamin A to membrane lipids and results in loss of vision.

[0010] RPE65 mutations are predominantly associated with early-onset severe retinal dystrophy, with rod-cone degeneration, nystagmus and severe visual loss within the first few years of life. The severity of the disease resulting from mutations in RPE65 appears to be largely independent of the mutation types present in the RP subjects. Many RPE65 subjects share a common phenotype characterized by poor but useful visual function in early life (measurable cone ERGs) that declines dramatically throughout the school age years. In addition, a number of these RP subjects retain residual islands of peripheral vision, although considerably compromised, into the third decade of life.

[0011] Progressive visual field (VF) loss is one of the hallmarks of RP and is commonly used

as a means to monitor the progression of the disease (Grover et al., Ophthalmology, 105: 1069-1075 (1998)). It has been observed that most RP subjects are legally blind by age 40 because of severely constricted visual fields due to loss of rod function exceeding reduction of cone sensitivity.

[0012] Visual acuity (VA) impairment may also be noted during the course of the RP although RP subjects with early-onset RP have been reported to have more stable VA than other RP types and the level of VA impairment can vary widely amongst RP subjects. For example, it has been reported for some RP patients with advanced RP with a small island of remaining central VF, that VA may remain normal. In other RP patients, VA decreases can be more pronounced.

[0013] By way of another example, Leber congenital amaurosis (LCA), a cause of inherited childhood blindness that affects children from birth or shortly thereafter, is associated with an inherited gene mutation, for example, in the RPE65 gene which encodes the protein retinal pigment epithelial protein 65 (RPE65) and/or an inherited gene mutation in the LRAT gene which encodes the enzyme lecithin:retinol acetyltransferase (LRAT). Patients with LCA lack the ability to generate 11-cis-retinal in adequate quantities and therefore suffer from severe vision loss at birth, nystagmus, poor pupillary responses and severely diminished electroretinograms (ERGs). Significant clinical variability in the severity of LCA presentation exists, including intrafamilial variability in severity. LCA exhibits clinical and genetic heterogenetity in terms of the natural history of vision loss, behavior in low light conditions, and genetic defects responsible for the phenotype.

[0014] Retinitis Punctata Albesciens (RPA) is another form of RP that exhibits a shortage of 11-cis-retinal in the rods. Recently, homozygous frameshift mutations in LRAT were identified as a cause of RPA in certain subjects and it has been reported that LRAT is the fourth gene involved in the visual cycle that may cause a white-dot retinopathy (Littink et al., Ophthalmology, 119: 1899-906 (2012)).

[0015] Congenital Stationary Night Blindness (CSNB) and Fundus Albipunctatus are a group of diseases that are manifested as night blindness, but there is not a progressive loss of vision as in RP. Some forms of CSNB are due to a delay in the recycling of 11-cis-retinal. Fundus Albipunctatus until recently was thought to be a special case of CSNB where the retinal appearance is abnormal with hundreds of small white dots appearing in the retina. It has been shown recently that this is also a progressive disease although much slower than RP. It is caused by gene defects that lead to a delay in the cycling of 11-cis-retinal, including heterozygous mutations in RPE65 (Schatz et al., Ophthalmology, 118:888-94 (2011)).

[0016] The use of synthetic retinal derivatives and compositions thereof in methods of restoring or stabilizing photoreceptor function in a vertebrate visual system is disclosed in WO 2004/082622, WO 2006/002097, WO 2009/102418, and WO 2011/034551, WO 2011/132084, and US 2004/0242704, US 2008/0221208 (issued as US Patent No. 7,951,841), and 2010/0035986 (issued as US 8,324,270). WO2011/034551A2 disclosed the use of 9-cis-retinyl acetate for the treatment of Leber congenital amaurosis. A study to evaluate the effects of daily

and intermittent dosing of 9-cis-retinyl acetate, a synthetic retinal derivative, in the treatment of retinopathy in RPE-deficient aging mice is disclosed in Maeda, T. et al., Investigative Ophthalmology & Visual Science (2009), Vol. 50, No. 9, pp. 4368-4378).

[0017] Animal models have shown that synthetic retinoids which are highly-light sensitive compounds are photoisomerized or "bleached" by light from the retina within just a few hours unless the eyes are covered. These studies were conducted with the animals kept in the dark for specified periods during treatment with synthetic retinoids until the evaluation period in order to minimize photoisomerization/bleaching of the synthetic retinoid, defeating the entire purpose of the treatment. Batten ML et al. "Pharmacological and rAAV Gene Therapy Rescue of Viscual Functions in a Blind Mouse Model of Leber Congenital Amaurosis" PLo-S Medicine vol. 2, p. 333 (2005); Margaron, P., Castaner, L., and Narfstrom, K. "Evaluation of Intravitreal cis-Retinoid Replacement Therapy in a Canine Model Of Leber's Congenital Amaurosis" Invest Ophthalmol Vis Sci 2009; 50:E-Abstract 6280; Gearhart PM, Gearhart C, Thompson DA, Petersen-Jones SM. "Improvement of visual performance with intravitreal administration of 9-cis-retinal in Rpe65-mutant dogs" Arch Ophthalmol 2010; 128(11): 1442-8.

[0018] Frequent administration of any retinoid to compensate for the bleaching effect implicates the well-known toxicity of the retinoid class of the compounds. See, Teelmann, K "Retinoids: Toxicity and Teratogenicity to Date," Pharmac. Ther., Vol. 40, pp 29-43 (1989); Gerber, LE et al "Changes in Lipid Metabolism During Retinoid Administration" J. Amer. Acad. Derm., Vol. 6, pp 664-74 (1982); Allen LH "Estimating the Potential for Vit A Toxicity in Women and Young Children" J. Nutr., Vol. 132, pp. 2907-19 (2002); Silverman, AK "Hypervitaminosis A Syndrome: A Paradigm of Retinoid Side Effects", J. Am. Acad. Derm., Vol. 16, pp 1027-39 (1987); Zech LA et al. "Changes in Plasma Cholesterol and Triglyceride Levels After Treatment with Oral Isotretinoin" Arch. Dermatol., Vol. 119, pp 987-93 (1983). Toxicity caused by chronic administration of retinoids can cause changes in lipid metabolism, damage to the liver, nausea, vomiting, blurred vision, damage to bones, interference with bone development and several other serious undesirable effects.

[0019] In the context of improving visual function in a subject with an endogenous retinoid deficiency, such as RP or LCA, which is a chronic condition requiring lifetime treatments, these toxic effects can be very important. These side effects are of particular concern in young subjects, whose susceptibility to side effects related to their physical development is well documented.

[0020] This combination of a need for repeated administration in response to bleaching, and the undesirable serious side effects of repeated administration, poses a problem for the use of synthetic retinoids to improve visual function in a subject having an endogenous retinoid deficiency, such as RP or LCA. A recent study evaluated the usefulness of retinoids as a treatment for these disorders and concluded that retinoids and similar compounds were not good therapeutic candidates. See, Fan J. et al. "Light Prevents Exogenous 11-cis Retinal from Maintaining Cone Photoreceptors in Chromophore-deficient Mice", Invest. Ophthalmol.Vis Sci. January 12, 2011, 10-6437.

Summary of Invention

[0021] The invention provides:

1. 1. A synthetic retinal derivative for use in improving visual function of a subject with an endogenous retinoid deficiency, by a method comprising:
    1. a. administering a first therapeutic dose of a synthetic retinal derivative, wherein the synthetic retinal derivative is 11-cis-retinyl acetate, 9-cis-retinyl acetate, or 9-cis-retinyl succinate, wherein the first therapeutic dose is administered as a divided dose over a period of from 2 to 7 days;
    2. b. providing a resting period of 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, or 27 days; and
    3. c. administering a second therapeutic dose of the synthetic retinal derivative to said subject following the end of the resting period,

   wherein the endogenous retinoid deficiency is retinitis pigmentosa (RP) or Leber congenital amaurosis (LCA).
2. 2. The synthetic retinal derivative for use of clause 1, wherein the subject has:
    1. (a) RP;
    2. (b) early onset or juvenile RP;
    3. (c) LCA; or,
    4. (d) a mutation in a gene selected from the LRAT or the RPE65 gene.
3. 3. The synthetic retinal derivative for use of clause 1 or 2, wherein the method further comprises repeating steps b and c one or more times.
4. 4. The synthetic retinal derivative for use of any of clauses 1-3, wherein the first therapeutic dose is administered:
    1. (a) as a divided dose over a period of 7 days;
    2. (b) as a divided dose over a period of 5 days; or,
    3. (c) as a divided dose over a period of 6 days, 4 days, 3 days, or 2 days.
5. 5. The synthetic retinal derivative for use of any of clauses 1-4, wherein the resting period is selected from:
    1. (a) an interval of 21 days;
    2. (b) an interval of 14 days.
6. 6. The synthetic retinal derivative for use of any of clauses 1-5, wherein the subject is a human subject.
7. 7. The synthetic retinal derivative for use of clause 6, wherein the human subject is an RP subject, wherein said RP subject is 15 years or older, 20 years or older, 30 years or older, 40 years or older, 50 years or older, or 60 years or older, when the therapeutic regimen is initiated.
8. 8. The synthetic retinal derivative for use of clause 6, wherein the human subject is an RP subject, wherein said subject is 50 years or less when the therapeutic regimen in initiated.

9. 9. The synthetic retinal derivative for use of any preceding clause, wherein the synthetic retinal derivative is 9-cis-retinyl acetate.
10. 10. The synthetic retinal derivative for use of any preceding clause, wherein the first therapeutic dose:
    1. (a) is from 280 mg/m^2 to 420 mg/m^2;
    2. (b) is 280 mg/m^2;
    3. (c) is 420 mg/m^2;
    4. (d) is 10 mg/m^2 per day;
    5. (e) is 20 mg/m^2 per day;
    6. (f) is 40 mg/m^2 per day; or,
    7. (g) is 60 mg/m^2 per day.
11. 11. The synthetic retinal derivative for use of any preceding clause, wherein the retinal derivative is for use in oral administration.

[0022] Improving visual function may comprise increasing visual field in an eye by at least 20% from baseline as measured by Goldmann Visual Field (GVF) analysis. Improving visual function may comprise increasing visual acuity in an eye by greater than or equal to 5 letters from baseline as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. Improving visual function may comprise a clinically significant increase in retinal sensitivity from baseline.

[0023] Specific embodiments of these aspects of the disclosure are described in more detail below.

Detailed Description of the Drawings

[0024]

Figure 1 provides a schematic drawing of the retinoid cycle.

Figure 2 shows GVF response as the proportion of eyes with an improvement over baseline in the intent to treat (ITT) (2A) and the per protocol subset (2B) of RP subject eyes at days 7, 14 and 30 after the first day of dosing.

Figure 3 shows GVF response based on VF severity (ITT; all subjects included). Figure 3A shows the proportion of eyes with greater than 20% improvement in GVF wherein the starting GVF is greater than 20 degrees at baseline (least severe), and Figure 3B shows the proportion of eyes with greater than 20% improvement in GVF wherein the starting GVF is only central and/or less than 20 degrees at baseline.

Figure 4 shows GVF response based on VF severity (Per protocol analysis; 3 subjects

excluded). Figure 4A shows the proportion of eyes with greater than 20% improvement in GVF wherein the starting GVF is greater than 20 degrees at baseline (least severe), and Figure 4B shows the proportion of eyes with greater than 20% improvement in GVF wherein the starting GVF is only central and/or less than 20 degrees at baseline.

Figure 5 provides GVF results to day 30 in a multilevel, mixed-effects model analysis of the percent change in retinal area from mean baseline calculated for all subjects (ITT) and the evaluable subset, excluding 3 subjects based on major, defined inclusion/exclusion criteria related to their GVF determinations.

Figure 6 shows GVF response (ITT) as the percent of GVF responders with response in both eyes, response in one or more eyes, or proportion of eyes responded wherein a responder is defined as patients/eyes for whom retinal area, relative to the mean baseline value, increased by at least 20% on 2 consecutive follow-up visits until month 1.

Figure 7 shows VA results as the mean VA change from baseline, ETDRS letter score, with improvements shown at Day 7, Day 14, or Month 1 for all subjects and the Evaluable subjects, excluding eyes which had baseline VA of zero letters.

Figure 8 shows VA response as the proportion of VA responders with eyes with greater than or equal to 5 letter improvement from baseline in both the ITT (8A) and the Evaluable (8B) subsets.

Figure 9 shows VA response (ITT) as the percent of VA responders with response in both eyes, response in one or more eyes, or proportion of eyes responded, wherein a responder is defined as having an improvement of greater than or equal to 5 ETDRS letters from baseline, or if baseline is zero, a responder is defined as anything above baseline, obtained in two consecutive visits until one month.

Figure 10 provide the overall summary of best change in visual acuity (VA) from baseline (ETDRS letter score) from Day 9 to Month 8 post dosing, wherein data has been clustered based on Baseline VA category.

Figure 11 shows the ETDRS / LogMAR / Snellen equivalent visual acuity (VA) for the eleven subjects of Figure 6 after treatment with either 40 mg/m2 (40mg) or 10 mg/m2 (10mg) of the Composition. Data represents the average letter score for both eyes, with the exception of Subjects 4 and 11, both of which demonstrated measurable letter scores for only one eye.

Figure 12 provides the AMA low vision grid analysis of the Goldmann visual fields (GVF) for Subjects 1-9 wherein analysis was performed of the GVFs observed with the small I4e target (OD) before and at Day 14.

Figure 13 provides the AMA low vision grid analysis of the Goldmann visual fields (GVF) for Subjects 1-9 wherein analysis was performed of the GVFs observed with the larger V4e target (OD) before and at Day 14.

Figure 14 shows the VA change from baseline in number of ETDRS letters, by quartile, for the

RP subjects as defined in Example 4.

Detailed Description of the Invention

[0025] The present disclosure provides synthetic retinal derivatives for improving visual function in a subject with an endogenous retinoid deficiency, such as those caused by mutations in the genes encoding the enzymes and proteins utilized in the visual cycle, such as RP or LCA. The synthetic retinal derivatives for improving visual function may be used to provide for efficacy while a clinically relevant safety profile is maintained. Divided dose herein refers to the total therapeutic dose divided over the number of days during the dosing period wherein the dose may be about the same on each day of dosing or the divided dose may be different. The therapeutic dose is administered over a period of about 2 to about 7 days. The resting period starts on the day following the last administration of the therapeutic dose. A clinically relevant safety profile is obtained upon repeated dosing with a resting period of less than 30 days. (See Example 5) This safety profile, in combination with a decline of visual function in some subjects, for example in certain RP subjects following administration of the first therapeutic dose after about day 7 to about day 30, indicates that a resting period of less than one month may be desirable. (See Example 2 and Figures 2-9) After a first therapeutic dose, visual function testing in certain subjects can identify candidates for early retreatment based on regression or lack of response in parameters of visual function.

[0026] The resting period may be 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, or 27 days. During the resting period a therapeutic dose of a synthetic retinoid derivative is not administered to the subject as part of this dosing regimen.

[0027] The second dose or subsequent doses are administered at any time following the end of the resting period. The second dose or subsequent doses may be the same as the first therapeutic dose, both in total administration of the synthetic retinal derivative, (mg/m^2) or duration of dosing period. The second or subsequent doses may be different than the first therapeutic dose, either in total amount of the synthetic retinal derivative, administered (mg/m^2) or in the duration of the dosing period.

[0028] The resting period and second administration of the synthetic retinal derivative can be repeated as needed to maintain the improvement in the subject's visual function achieved during the first dosing period. It is understood that endogenous retinoid deficiencies, such as RP and LCA, are a chronic conditions, due at least to gene mutations resulting in loss of function of endogenous 11-cis retinal, and that additional dosing beyond the first dose, resting period and second dose may be needed to maintain improvement in the visual function of the subject. It is the combination of the therapeutic dose (amount and duration) with the resting period that provides for a clinically relevant improvement of visual function for a condition

associated with an endogenous retinoid with a clinically relevant safety and efficacy profile.

[0029] The amount of the therapeutic dose (first, second or subsequent) can be designated either as the total amount administered for a particular dose or as an amount administered over the time period for a particular dose (e.g., first dose or second dose). In one aspect, the synthetic retinal derivative, being administered to the subject having an endogenous retinoid deficiency, such as RP or LCA, is 9-cis retinyl acetate, as used in the composition of Example 1, or 11-cis retinyl acetate.

[0030] The subject having an endogenous retinoid deficiency, such as RP or LCA, being administered a synthetic retinoid derivative can be categorized as having mild, moderate or severe visual impairment based on visual acuity and visual field measurements. Based on World Health Organization (WHO), ICD-9-CM, and Medicare benefits criteria, normal vision is defined as a subject with a visual acuity of less than 20/25 and normal visual field, which extends to approximately 60 degrees nasally (toward the nose, or inward) in each eye, to 100 degrees temporally (away from the nose, or outwards), and approximately 60 degrees above and 75 below the horizontal meridian. Mild vision loss is defined as a subject with a visual acuity of 20/30 - 20/65. Moderate vision loss is defined as a subject with a visual acuity of 20/70 - 20/190 and a visual field of greater than 20 degrees. Severe vision loss is defined as a subject with a visual acuity of 20/200-20/490 and a visual field of 20 degrees or less. Profound vision loss is defined as a subject with a visual acuity of 20/500-20/1000 and a visual field of 10 degrees or less. Near blindness is defined as a visual acuity of 20/1100-20/2000 and a visual field of 5 degrees or less. Total blindness is defined as a subject with no light perception.

[0031] The subject may have RP and have been categorized as having moderate to severe RP, mild RP or mild to moderate RP.

[0032] In one aspect, the improvement in a subject's visual function may be measured as a function of baseline. A baseline may be determined for each subject or it may be determined for a group of subjects. A baseline may not be individually determined for a subject but a baseline from a similar group of subjects may be applied to an individual subject.

[0033] The baseline of the subject's visual function may be established prior to the administration of the first therapeutic effective dose of the synthetic retinal derivative, by evaluating one or more of the subject's visual field, visual acuity, ability to perform life tasks, retinal sensitivity, dynamic pupillary response, nystagmus, cortical visual function, color vision or dark adaptation. The baseline of the subject's visual function may be established by evaluating the subject's field of vision, visual acuity or retinal sensitivity. The baseline may be established by evaluating the subject's visual field, visual acuity and retinal sensitivity.

[0034] Establishing the subject's baseline of visual function may comprise establishing a baseline of one or more of the subject's visual field, the subject's visual acuity, the subject's retinal sensitivity, the subject's dynamic pupillary response, the subject's nystagmus, the subject's cortical visual function, the subject's ability to perform life tasks, the subject's color

vision and the subject's dark adaptation. Preferably, establishing the subject's baseline of visual function comprises establishing the baseline of the subject's visual field, the subject's visual acuity, the subject's ability to perform life tasks, and the subject's retinal sensitivity by established tests.

[0035] The subject's visual function may improve rapidly within the dosing period from the baseline of the subject's visual function established prior to administration of the first therapeutic effective amount of the synthetic retinal derivative. For purposes of this disclosure, "rapidly improves" refers to a clinically meaningful improvement in a subject's visual functions as compared to the baseline of the subject's visual functions in a period shorter than the first dosing period. Preferably, the subject's visual functions are significantly improved within one week of the commencement of the dosing period. The subject's visual functions may improve during the dosing period as compared to baseline, and remain above baseline after the completion of the first dosing period and into the resting period. The improvement in the subject's visual function in the first dosing period may comprise expanding the subject's visual field as compared to the visual field baseline, improving the subject's visual acuity as compared to the visual acuity baseline, and/or improving the subject's retinal sensitivity as compared to the baseline retinal sensitivity.

[0036] The improvement in the subject's visual function may comprise an expansion of the subject's visual field or one or more eyes as compared to the baseline. The improvement in the subject's visual function during the first dosing period may comprise increasing visual field in one or more eyes of the subject by at least 30%, 25%, 20% or 15% from baseline as measured by Goldmann Visual Field (GVF) analysis. The improvement in the subject's visual function may comprise increasing visual field in an eye of the subject by at least 20% from baseline as measured by Goldman Visual Field analysis.

[0037] The improvement in the subject's visual function in one or more eyes may comprise an improvement in the subject's visual acuity as compared to the baseline. The improvement in the subject's visual function may comprise increasing visual acuity in one or more eyes of the subject by greater than or equal to 5 letters from baseline as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.

[0038] The improvement in the subject's visual function in one or more eyes in the first dosing period may comprise an improvement in the subject's retinal sensitivity in one or more eyes as compared to the baseline.

[0039] The improvement in the subject's visual function in the resting period may comprise an improvement in the subject's retinal sensitivity in one or more eyes as compared to the improvement in the subject's retinal sensitivity during the first dosing period.

[0040] The improvement in the subject's visual function may comprise an improvement in the RP subject's dark adapted perimetry from baseline in one or more eyes.

[0041] In some embodiments, the resting period is from 14 days to 21 days. In certain embodiments, the resting period is 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, or 27 days.

[0042] Dosing regimens that combine a clinically relevant safety profile in combination with a plurality of therapeutic dosing periods and resting periods may be established. Up to 6, up to 5, up to 4, or up to 3 therapeutic doses may be administered in up to 6 months, up to 5 months, up to 4 months or up to 3 months. Up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, or up to 3 therapeutic doses may be administered to a subject in up to 12 months, up to 11 months, up to 10 months, up to 9 months, up to 8 months, up to 7 months, up to 6 months, up to 5 months, up to 4 months, or up to 3 months. Up to 3 therapeutic doses may be administered in about 3 months. Up to 6 therapeutic doses may be administered in about 6 months. In certain instances of the foregoing, no more than one therapeutic dose is administered per month.

[0043] The resting time period may be the period after which the subject's triglyceride levels and or HDL levels, cholesterol levels, and LDL levels have returned to clinically safe and acceptable levels, prior to administering a subsequent therapeutic dose.

[0044] In some embodiments, the subject's loss of vision is due to a LRAT or RPE65 gene mutation. The subject may have one or more LRAT gene mutations, one or more RPE65 gene mutations, one or more null or missense LRAT mutations or one or more null or missense RPE65 mutations.

[0045] The subject may have autosomal recessive retinitis pigmentosa (arRP), or autosomal dominant retinitis pigmentosa (adRP). The subject may have early-onset RP or juvenile RP.

[0046] The first and any subsequent therapeutic effective amount may be administered orally to the subject having an endogenous retinoid deficiency, such as RP or LCA.

[0047] The synthetic retinal derivative can be delivered by any pharmacological vehicle in which it is stably delivered to the subject having an endogenous retinoid deficiency, such as RP or LCA, and effectively released upon administration. The pharmaceutical vehicle art is well familiar with the chemistry of retinoids and the formulations of pharmacological vehicles for them. These known delivery vehicles include those which have physical properties, chemical properties and release rates that are suited to delivery synthetic retinal derivatives. Liquid delivery vehicles, such as vegetable oils (including soybean, olive, and rapeseed or canola oils) can be used.

[0048] The synthetic retinal derivative is selected from 11-cis-retinyl acetate, 9-cis-retinyl acetate or 9-cis-retinyl succinate.

[0049] A pharmaceutically acceptable composition may comprise the synthetic retinal derivative and soybean oil. A pharmaceutically-acceptable composition may comprise a 9-cis-

retinyl acetate and soybean oil, which may be soybean oil (USP grade).

[0050] A pharmaceutical composition may further comprise an antioxidant. A pharmaceutically-acceptable composition may comprise 9-cis-retinyl acetate, soybean oil, and butylated hydroxyanisole (BHA). A pharmaceutically-acceptable composition may comprise 9-cis-retinyl acetate, soybean oil (USP grade), and butylated hydroxyanisole (BHA).

[0051] Unless defined otherwise in the specification, the following terms and phrases shall have the following meanings:
As used herein, "visual disorders" refers broadly to disorders in the photoreceptors, tissue or structures of the eye. Visual disorders include retinal degeneration, retinal dystrophy, loss of photoreceptor function, photoreceptor cell death and structural abnormalities. Visual disorders of the disclosure are typically characterized by impaired or less than normal (including complete loss of) visual functions in a subject, which include, for example, poor visual acuity, low or lack of retinal sensitivity, narrow or undetectable visual fields.

[0052] "Therapeutically effective amount" refers to that amount of a compound which, when administered to a subject having an endogenous retinoid deficiency, preferably a human, is sufficient to cause a clinically meaningful therapeutic effect.

[0053] The term "therapeutic effect" as used herein refers to the improvement of the vision of a subject, in one or both eyes of the subject, wherein an improvement in the subject's visual function in one or both eyes during a therapeutic regimen of the disclosure can be demonstrated by comparing the subject's visual functions of one or both eyes with a baseline measure of the subject's visual functions of one or both eyes prior to administration of a therapeutic regimen of the disclosure or by comparing the subject's visual functions of one or both eyes with a comparable human visual system not receiving the therapeutic regimen.

[0054] The loss of vision in RP subjects with retinoid deficiency is typically severe, but can be present in degree and forms that vary from RP subject to RP subject. Subjects can lose their peripheral vision, they can lose their ability to see in low to moderate light, their overall acuity can decline, or other vision loss can occur. This loss can be progressive (especially in adult onset case(s) of retinoid deficiency) eventually leading to very little vision or to complete blindness.

[0055] The type and extent of loss can be roughly correlated to the degree of retinoid deficiency, affected cell type (e.g. rods or cones), and/or localization of the retinoid deficiency in the retina. Where the deficiency effect is strongest at the periphery of the retina, peripheral vision losses can be seen earliest and most profoundly. When the deficiency effect is more generalized throughout the retina, an overall loss of acuity is more commonly observed. When the deficiency is great or of long standing, the vision loss (in whatever form) can be more severe and more difficult to successfully improve. Because the nature and degree of vision loss caused by the retinoid deficiency disorder varies from subject to subject, the nature and degree of meaningful improvement of vision will also vary from subject to subject. For example,

regaining the ability to see in moderate light can be a meaningful improvement that is manifested in some subjects, for example in some RP patients. For other subjects, for example in some RP patients, a meaningful improvement will be to enhance peripheral vision, or a general improvement in acuity. Progressive loss of vision may be arrested or reversed by this disclosure. However, in cases where diagnosis and therapeutic intervention occur early, administration of a dosing regimen according to this disclosure may simply limit or slow the progression of vision loss.

[0056] Clinically meaningful improvements can be documented by any of several known clinical measures discussed in this application, including acuity, field of vision, light sensitivity, the ability to perform life tasks or a combination of some or all of these. These measures and others are all well known to the clinicians and are routinely used in clinical practice. Clinicians are easily able to identify and observe these changes as part of routine clinical evaluations of subject with visual disorders associated with an endogenous retinoid deficiency, including RP and LCA subjects. Consequently, clinicians are also easily able to observe the identify improvements in vision that are meaningful in the context of a given subject.

Visual disorders associated with Endogenous Retinoid Deficiency

[0057] The therapeutic regimens and methods of the disclosure are for the improvement of visual function in a subject, having loss of visual functions due to endogenous retinoid deficiency. The visual disorders may be inherited retinal diseases (IRD) caused by gene mutations that disrupt or interfere with the production, conversion and/or regeneration of 11-cis-retinal, resulting in visual impairment or blindness. Such deficiencies are characterized by an absent, deficient or depleted level of one or more endogenous retinoids, such as 11-cis-retinal. Thus, "endogenous retinoid deficiency" refers to prolonged lower levels of endogenous retinoids as compared to the levels found in a healthy eye of a subject of the same species. In some cases, a healthy eye of a subject may experience transient shortage of 11-cis-retinal, which leads to a brief period of blindness followed by vision recovery, while in subjects with an endogenous retinoid deficiency, the subject is deficient in its ability to reliably or rapidly regenerate the endogenous level of 11-cis-retinal, which leads to prolonged and/or pronounced 11-cis retinal deficits.

[0058] Therapeutic regimens and methods of the disclosure are for the improvement of visual function in a subject, having an inherited retinal disorder, such as RP, LCA and subtypes thereof.

[0059] Endogenous retinoid deficiency can be caused by one or more defects in the visual cycle which includes enzymatic deficiencies and impaired transport processes between the photoreceptors and retinal pigment epithelial cells (RPE). Figure 1 schematically shows a vertebrate, preferably the human, visual cycle (or retinoid cycle), which operates between the RPE and the outer segments of photoreceptors. 11-cis-retinal is regenerated through a series of enzymatic reactions and transport processes to and from the RPE after which it binds to

opsin to form rhodopsin in the photoreceptor. Rhodopsin is then activated by light to form meta-rhodopsin which activates the phototransduction cascade while the bound cis-retinoid is isomerized to all-trans-retinal (von Lintig, J. et al., Trends Biochem Sci Feb 24 (2010)).

[0060] Mutations in more than a dozen genes encoding retinal proteins have been identified that participate in several biochemical pathways in the visual cycle. For example, mutations in genes that encode lecithin:retinoid acetyl transferase (the LRAT gene) and retinal pigment epithelium protein 65 kDa (the RPE65 gene) disrupt the retinoid cycle, resulting in a deficiency of 11-cis-retinal, an excess of free opsin, an excess of retinoid waste (e.g., degradation) products and/or intermediates in the recycling of all-trans-retinal, or the like.

[0061] Endogenous retinoid levels in a subject's eyes, for example an RP or LCA subject's eyes, and deficiencies of such levels may be determined in accordance with the methods disclosed in, for example, US . 2005/0159662. Other methods of determining endogenous retinoid levels in a vertebrate eye and a deficiency of such retinoids include, for example, analysis by high pressure liquid chromatography (HPLC) of retinoids in a blood sample from a subject. For example, a blood sample can be obtained from a subject and retinoid types and levels in the sample can be separated and analyzed by normal phase high pressure liquid chromatography (HPLC) (e.g., with a HP 1100 HPLC and a Beckman, Ultrasphere-Si, 4.6 mm x 250 mm column using 10% ethyl acetate/90% hexane at a flow rate of 1.4 ml/minute). The retinoids can be detected by, for example, detection at 325 nm using a diode-array detector and HP Chemstation A.03.03 software. A deficiency in retinoids can be determined, for example, by comparison of the profile of retinoids in the sample with a sample from a control subject (e.g., a normal subject).

[0062] Various conditions can cause a subject to be predisposed to or develop endogenous retinoid deficiency. For example, a subject that has an RPE65 gene mutation or an LRAT gene mutation is genetically predisposed to endogenous retinoid deficiency and visual impairment that ultimately lead to complete vision loss and severe retinal dystrophy. In particular, RPE65 and LRAT gene mutations are found in RP and LCA subjects.

[0063] RP can be caused by defects in many different genes with more than 200 causative RP mutations detected in more than 100 different genes to date. RP genotypes are heterogeneous, and RP subjects with the same mutation can exhibit different phenotypes. RP may be inherited by autosomal dominant, autosomal recessive, or X-linked traits. In recent years, mutations in the LRAT and RPE65 genes have been discovered in RP subjects with arRP or adRP. These specific mutations are linked to defects in retinoid metabolism of the visual cycle and may result in photoreceptor degeneration.

[0064] As noted herein, the protein encoded by the RPE65 gene has a biochemical association with retinol binding protein and 11-cis-retinol dehydrogenase and is essential for 11-cis-retinal production (Gollapalli, D.R. et al., Biochemistry. 42(19):5809-5818 (2003) and Redmond, T.M. et al., Nat Genet. 20(4):344-351 (1998)). Preclinical and clinical information show that loss of the function of the RPE65 protein blocks retinoid processing after esterification of vitamin A to

membrane lipids and results in loss of vision.

[0065] RPE65 mutations are predominantly associated with early-onset severe retinal dystrophy, with rod-cone degeneration, nystagmus and severe visual loss within the first few years of life. The severity of the disease resulting from mutations in RPE65 appears to be largely independent of the mutation types present in the patients. Many RPE65 patients share a common phenotype characterized by poor but useful visual function in early life (measurable cone ERGs) that declines dramatically throughout the school age years. In addition, a number of these patients retain residual islands of peripheral vision, although considerably compromised, into the third decade of life.

[0066] Progressive visual field (VF) loss is one of the hallmarks of RP and is commonly used as a means to monitor the progression of the disease. It has been observed that most RP subjects are legally blind by age 40 because of severely constricted visual fields due to loss of rod function exceeding reduction of cone sensitivity.

[0067] Visual acuity (VA) impairment may also be noted during the course of the RP although RP subjects with early-onset RP have been reported to have more stable VA than other RP types and the level of VA impairment can vary widely amongst RP subjects. For example, it has been reported for some RP patients with advanced RP with a small island of remaining central VF, that VA may remain normal. In other RP patients, VA decreases can be more pronounced.

Subject Populations

[0068] While a subject having a visual disorder associated with an endogenous retinoid deficiency (as defined herein) may be treated by the therapeutic regimens and methods of the disclosure, there may be a physiological window of opportunity wherein the therapeutic regimen or method is the most effective in slowing the rate of decline or improving visual function to the subject. The window of opportunity for the therapeutic regimens of the disclosure to be the most effective in a subject may be defined as the interval between loss of visual function and retinal degeneration, particularly with respect to photoreceptor cell degeneration. Subjects in certain age groups may particularly benefit from the therapeutic regimens of the disclosure. More specifically, subjects with a lesser degree of retinal/photoreceptor degeneration tend to have a better or faster response to the therapeutic regimen of the disclosure and/or may have a longer resting period before a subsequent dosing period is needed. For example, younger subjects with a loss of visual function due to an endogenous retinal deficiency, such as LCA or RP, may retain a higher percentage of dormant photoreceptors. Such dormant photoreceptors are capable of responding to the therapeutic regimens of the invention. In particular, in improving visual function in a subject arising from inherited childhood blindness such as LCA or early onset RP, such as arRP, younger subjects may expect a greater recovery of visual functions because their retinal degeneration is less advanced.

[0069] In some instances, RP may appear in a human subject during the second decade or even later. The average age of diagnosis for arRP in a human is about 36 years old (Tsujikawa M. et al., Arch Ophthalmol 126(3) 337-340 (2008)). Thus, the human RP subject may be 15 years old or older, 20 years old or older, 30 years old or older, 40 years or older, 50 years or older, or 60 years or older when the therapeutic regimen is initiated.

[0070] For any of these subjects, the therapeutic regimens and methods of the disclosure should commence as soon as a diagnosis of a visual disorder as defined herein is ascertained, such that any degeneration of the retina, in particular the photoreceptors, has not reached a point where the therapeutic regimens of the disclosure would be ineffective in improving visual function in the subject.

Synthetic Retinal Derivatives

[0071] Synthetic retinal derivatives can be administered to improve visual function, and/or to ameliorate the effects of a deficiency in retinoid levels. A synthetic retinoid can be administered prophylactically (e.g., to a subject diagnosed with an endogenous retinoid deficiency, to prevent, slow, or delay deterioration or further deterioration of the subject's visual function, as compared to a comparable subject not receiving the synthetic retinoid) or therapeutically to a subject.

[0072] Without intending to be bound by any particular theory, it is believed that the synthetic retinal derivatives used in the therapeutic regimens of the disclosure provide replacements for endogenously produced 11-cis-retinal, thereby restoring the key biochemical component of the visual cycle. A synthetic retinal derivative suitable for the therapeutic regimens of the disclosure can be a derivative of 9-cis-retinal or 11-cis-retinal. Like 11-cis-retinal, 9-cis-retinal can bind to opsin to form photoactive isorhodopsin which, when bleached, undergoes conformational changes via the same photoproducts as 11-cis-retinal regenerated rhodopsin (Yoshizawa, T. et al., Nature 214, 566-571 (1967) and Filipek S. et al., Annu Rev Physiol 65:851-79 (2003)). 9-cis-retinal and its derivatives are generally more thermodynamically stable than their 11-cis retinal counterparts.

[0073] The synthetic retinal derivatives can be converted directly or indirectly into a retinal or a synthetic retinal analog. Thus, in some aspects, the compounds according to the present disclosure can be described as pro-drugs, which upon metabolic transformation are converted into 9-cis-retinal, 11-cis-retinal or a synthetic retinal derivative thereof. Metabolic transformation can occur, for example, by acid hydrolysis, esterase activity, acetyltransferase activity, dehydrogenase activity, or the like. For example, without wishing to be bound by theory, it is thought that a synthetic 9-cis-retinal derivative (e.g., a 9-cis-retinyl ester, such as 9-cis-retinyl acetate), is converted to 9-cis-retinol in the alimentary pathway, transported to the retina through the bloodstream and converted to 9-cis-retinal in the RPE.

[0074] 9- and 11-cis-retinyl esters are described in WO 2006/002097 and US . 2010/0035986.

The synthetic retinal derivatives can directly, or via a metabolite thereof, bind to opsin and function as an opsin agonist. As used herein, the term "agonist" refers to a synthetic retinal derivative that binds to opsin and facilitates the ability of the opsin/synthetic retinal derivative complex to respond to light. As an opsin agonist, a synthetic retinal derivative can create a pharmacological bypass of a blocked retinoid cycle, thus sparing the requirement for endogenous retinoid (e.g., 11-cis-retinal).

[0075] In certain embodiments, the 9- or 11-cis-retinyl ester for use in the present invention is not a naturally occurring retinyl ester normally found in the eye. In some embodiments, the 9- or 11-cis-retinyl ester is an isolated retinyl ester. As used herein, "isolated" refers to a molecule that exists apart from its native environment and is therefore not a product of nature. An isolated molecule may exist in a purified form or may exist in a non-native environment. Suitable synthetic 9-cis retinyl esters are 9-cis-retinyl acetate and 9-cis-retinyl succinate. In certain embodiments, the 9-cis-retinyl ester is 9-cis-retinyl acetate.

[0076] A suitable synthetic 11-cis retinyl ester is 11-cis-retinyl acetate.

[0077] The 9-cis-retinyl esters can be converted by the liver to a metabolic pro-drug form, namely fatty acid 9-cis-retinyl esters, which are stored in the liver in hepatic lipid droplets. Fatty acid 9-cis-retinyl esters and retinol are mobilized from the liver and enter the circulation where they travel to the eye and RPE. There, they are converted to 9-cis-retinal which ultimately combines with photoreceptor opsins to form active visual pigments.

[0078] A preferred 9-cis-retinyl ester is 9-cis-retinyl acetate. Also referred to as "9-cis-R-Ac", 9-cis-retinyl acetate is which is metabolized by the liver to fatty acid 9-cis-retinyl esters, such as 9-cis-retinyl palmitate. Fatty acid 9-cis-retinyl esters and retinol are then converted to 9-cis-retinal in the eye and RPE as replacement of deficient chromophores such as 11-cis-retinal.

[0079] 9-cis-R-Ac can be prepared by initially converting all-trans-retinyl acetate (Sigma-Aldrich) to a mixture of 9-cis-retinyl acetate and all-trans-retinyl acetate in the presence of a palladium catalyst (e.g., palladium salts, palladium oxides). The mixture of 9-cis-retinyl acetate and all-trans-retinyl acetate are then hydrolyzed to produce a mixture of 9-cis-retinol and all-trans-retinol. The pure 9-cis-retinol can be isolated by selective recrystallization and further esterified to pure 9-cis-R-Ac. A detailed description of the processes for preparing and purifying 9-cis-R-Ac can be found, for example, in GB 1452012.

[0080] The 9-cis-retinyl esters described herein can be prepared from 9-cis-retinol using appropriate esterifying agents in a manner similar to the preparation of 9-cis-R-Ac, the methods of which are within the knowledge of one skilled in the art.

[0081] 9- and 11-cis-retinyl esters can be formed by methods known in the art such as, for example, by acid-catalyzed esterification of a retinol with a carboxylic acid, by reaction of an acyl halide with a retinol, by transesterification of a retinyl ester with a carboxylic acid, by reaction of a primary halide with a carboxylate salt of a retinoic acid, by acid-catalyzed reaction

of an anhydride with a retinol, or the like. 9- and 11-cis-retinyl esters can be formed by acid-catalyzed esterification of a retinol with a carboxylic acid, such as, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, pelargonic acid, capric acid, lauric acid, oleic acid, stearatic acid, palmitic acid, myristic acid, linoleic acid, succinic acid, fumaric acid or the like. Retinyl esters can be formed by reaction of an acyl halide with a retinol (see, e.g., Van Hooser et al., Proc. Natl. Acad. Sci. USA, 97:8623-28 (2000)). Suitable acyl halides include, for example, acetyl chloride, palmitoyl chloride, or the like.

[0082] Trans-retinoids can be isomerized to cis-retinoids by exposure to UV light. For example, all-trans-retinal, all-trans-retinol, all-trans-retinyl ester or all-trans-retinoic acid can be isomerized to 9-cis -retinal, 9-cis-retinol, 9-cis-retinyl ester or 9-cis -retinoic acid, respectively. Trans-Retinoids can be isomerized to 9-cis-retinoids by, for example, exposure to a UV light having a wavelength of about 365 nm, and substantially free of shorter wavelengths that cause degradation of cis-retinoids.

[0083] The synthetic retinal derivative of the disclosure can be substantially pure in that it contains less than about 5% or less than about 1%, or less than about 0.1%, of other retinoids. One or more synthetic retinal derivatives may be used in the therapeutic regimens of the disclosure.

Pharmaceutically Acceptable Compositions of the Disclosure

[0084] Synthetic retinal derivatives, including 9- and 11-cis-retinyl esters, of the disclosure can be formulated for oral administration using pharmaceutically acceptable vehicles as well as techniques routinely used in the art. The synthetic retinal derivative may be formulated into a formulation suitable for oral administration. Most of the synthetic retinal derivatives are oily substances and lipophilic and are therefore easily miscible with one or more lipid vehicles.

[0085] Synthetic retinal derivatives, including 9- and 11-cis-retinyl esters, of the disclosure (e.g., 9-cis-retinyl esters) are light- and oxygen-sensitive. It is therefore desirable to maintain the stability and maximize the efficacy and shelf-life of the formulation. A suitable lipid vehicle may be selected based on its ability to stabilize the synthetic retinal derivatives suspended or solubilized therein. As used herein, "lipid" or "lipid vehicle" refers to one or a blend of fatty acid esters. The lipid vehicle may comprise one or more triglycerides, which are formed when a single glycerol is esterified by three fatty acids. Triglycerides include both vegetable oils and animal fats. The lipid vehicle may comprise more than 50 w/w% polyunsaturated fatty acids, the polyunsaturated fatty acids including an omega-6 fatty acid and an omega-3 fatty acid in a ratio (by weight) of less than 15.

[0086] The synthetic retinal derivatives, for example 9- or 11-cis-retinyl esters, may be formulated into an oral formulation comprising a retinal derivative, such as a 9- or 11-cis-retinyl ester, and a lipid vehicle. The 9- or 11-cis-retinyl ester may be 9-cis-retinyl acetate, and the lipid vehicle may be soy bean oil. The formulation may further comprise an antioxidant. The

antioxidant may be butylated hydroxyanisole (BHA). The description of additional lipid vehicles and formulations suitable for use can be found in, for example, International Patent Application No. PCT/US2009/059126 in the name of QLT Inc..

[0087] The present disclosure also provides kits that contain a synthetic retinal derivative, preferably a 9- or 11-cis-retinyl ester or a pharmaceutically acceptable composition thereof. The kit also includes instructions for the use of the synthetic retinal derivative in the therapeutic regimens and methods of the disclosure. Preferably, a commercial package will contain one or more unit doses of the synthetic retinal derivative, for example, one or more unit doses of a 9- or 11-cis-retinyl ester or the pharmaceutically acceptable composition for use in a therapeutic regimen or method of the disclosure. It will be evident to those of ordinary skill in the art that the synthetic retinal derivative, for example a 9- or 11-cis-retinyl ester or pharmaceutically acceptable compositions thereof which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used for the kit which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable excipients.

Dosage, Dosage Frequency and Modes of Administration

[0088] The synthetic retinal derivatives and pharmaceutically acceptable pharmaceutical compositions comprising the synthetic retinal derivatives used in the therapeutic regimens of the disclosure may be in the form of an oral dose. A pharmaceutically acceptable composition of the disclosure comprising a 9- or 11-cis-retinyl ester and a lipid vehicle may be administered orally to the subject in the therapeutic regimen of the disclosure. An orally-administered pharmaceutically acceptable composition of the disclosure may comprise a 9-cis-retinyl ester and soybean oil. An orally-administered pharmaceutically acceptable composition may comprise 9-cis-retinyl acetate or 9-cis-retinyl succinate and soybean oil (USP grade).

[0089] Oral administration of the synthetic retinal derivative, for example a 9- or 11-cis-retinyl ester, of the disclosure has several potential advantages, including exposure of all photoreceptors in both eyes of the subject undergoing the therapeutic regimen of the disclosure to therapy, lack of surgical intervention, and cessation of administration at any time. Therapeutic regimens of the disclosure may be used in combination with vector-mediated gene transfer therapy for replacement of one or more genes, for example, RPE65 or LRAT, associated with the visual cycle in a subject, for example in subjects who have already received gene therapy as a method for treating or ameliorating visual disorders associated with endogenous retinoid deficiency in a subject.

[0090] The therapeutic regimens of the present disclosure produce meaningful improvement of visual function, while exhibiting an acceptable safety profile, in, and thus, the therapeutic regimens of the present disclosure may be suitable as a long-term (chronic) therapeutic regimen.

[0091] The length of the resting period of time between the first therapeutic dose and the

second therapeutic dose is less than one month, and may be optionally selected be based on the persistence or increase in one or more of the subject's visual function parameters, as defined herein during the less than one month resting period. Dosing-dependent effects or improvement in the subject's visual functions may be observed and assessed on an individual basis to allow for customization of the subject's dosing requirements within the less than one month resting period. Alternatively, administration of a second therapeutic dose may be based on a decrease in one or more of the subject's visual function parameters relative to previous efficacy assessments during a first dosing period and any resting period. For instance, the efficacy of the subject's dosing may be assessed at, for example, about 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days or 21 days following the first therapeutic dose. At any point of the assessment, a subsequent therapeutic dose may be administered based on a regression of one or more of the subject's visual function parameters during any resting period.

[0092] The clinically relevant safety profile in combination with a plurality of therapeutic dosing periods and resting periods may be established. Up to 6, up to 5, up to 4, or up to 3 therapeutic doses may be administered in up to 6 months, up to 5 months, up to 4 months or up to 3 months. Up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, or up to 3 therapeutic doses may be administered to a subject in up to 12 months, up to 11 months, up to 10 months, up to 9 months, up to 8 months, up to 7 months, up to 6 months, up to 5 months, up to 4 months, or up to 3 months. Up to 3 therapeutic doses may be administered in about 3 months. Up to 6 therapeutic doses may be administered in about 6 months. In certain instances of the foregoing, no more than one therapeutic dose is administered per month.

[0093] The therapeutic regimens and methods established for an RP subject may be applied to an LCA subject.

[0094] Following oral administration of the composition, without wishing to be bound by any particular theory, it is believed that the drug is incorporated into lipid droplets in the liver and in the RPE (called retinosomes) from which it is mobilized. Imanishi Y. et al. J Cell Biol 166:447-53 (2004). It is secreted by the liver bound to retinol binding-protein 4 (RBP4) and delivered to peripheral tissues, whereas in the eye it is oxidized to 9-cis-retinal which feeds back into the retinoid cycle (Figure 1). Moise A.R. et al. Biochemistry 46:4449-58 (2007). Retinols, regardless of their isomeric form, are also stored in adipocytes and mobilized as needed into the circulation. O'Byrne S.M. et al. J Biol Chem 280:35647-57(2005). Thus, the long-term effects of this chromophore analog may derive from the fact that active drug is slowly released from adipocytes in the periphery.

Evaluation of Therapeutic Effect

[0095] The effectiveness of the therapeutic regimens of the disclosure in improving visual function in a subject with RP or LCA or with other visual disorders associated with an

endogenous retinoid deficiency, can be evaluated based on several measures of vision function, including those as described below.

[0096] Improvements in the subject's visual functions in one or both eyes may be evaluated based on measures of visual field, visual acuity, and retinal sensitivity testing, as well as electroretinograms, dynamic pupillary response, nystagmus, cortical visual function, color vision, visual mobility testing, and patient-reported outcomes of quality of life/ability to perform life tasks. The degree of retinal and photoreceptor degeneration can be further evaluated by optical coherence topography (OCT) and fundus autofluorescence (FAF) analysis at baseline and post-treatment. Improvements in the subject's visual functions in one or both eyes during a therapeutic regimen of the disclosure can be demonstrated by comparing the subject's visual functions of each eye with a baseline measure of the subject's visual functions of each eye prior to administration of a therapeutic regimen of the disclosure or by comparing the subject's visual functions of each eye with a comparable human visual system not receiving the therapeutic regimen.

1. Visual Field

[0097] Progressive visual field loss is one of the hallmarks of endogenous retinoid deficiencies, for example RP and LCA, and is commonly used as a means to monitor the progression of the disease. For example, it has been reported that most RP subjects are legally blind because of severely constricted visual fields.

[0098] Visual field is an individual's entire scope of vision, including the central and peripheral (side) vision of each eye. Normal human visual field extends to approximately 60 degrees nasally (toward the nose, or inward) in each eye, to 100 degrees temporally (away from the nose, or outwards), and approximately 60 degrees above and 75 below the horizontal meridian.

[0099] Visual field can be tested by art-recognized techniques and standards, such as Kinetic Perimetry by Goldmann Visual Field testing (GVF), Fundus Controlled Perimetry (Microperimetry - MP1), or Static Perimetry by Humphrey Visual Field Analyzer (HFA). GVF as generally measured on a standard calibrated Goldmann perimeter. Fields are measured by moving a stimulus (isopter or target) from nonseeing to seeing regions, thereby generating a map of peripheral visual field locations. Due to planimetric distortion in the testing procedure, GVF chart results may be digitized and converted to retinal surface area to most accurately capture changes in the peripheral VF in subjects with retinal degeneration. Baseline measures may be used to identify one VF isopter which provided a VF log retinal area closest to the midpoint 1.5 log mm^2 of the 0.7 to 2.4 log mm^2 range, for assessment of VF over time. Changes in log retinal area of the selected isopter size may be assessed using a mixed effects model which uses the log retinal area from each eye. Correlation and extent of the correlation between the two eyes of the same subject were accounted for in the analysis. Improvements in

visual field of greater than 20% are accepted as clinically significant improvements based on evaluation of test-retest variability (Bittner et al., IOVS 52:8042-8046 (2011)). VF may also be calculated as a solid angle measure in steradians, as a volume measure, combining the results of 2 or more isopters, or as an approximate Hill of Vision for 3 or more sequential isopters by finding the volume of the stacked isopters (Christoforidis, Clin. Ophthalmol., 5: 535-541 (2011)). Changes in visual field calculated by any method may be determined by comparison to the subject's baseline measures.

[0100] Subjects having the endogenous retinoid deficiencies described herein may have various degrees of impairments that can span from non-detectable to significantly contracted visual field. For example, identifiable, distinctive patterns of VF loss in RP subjects has been defined (Grover et al., Ophthalmology 105:1069-1075 (1998)). Typical, less advanced RP may demonstrate a VF > 20 degrees detectable with the V4e target. Atypical RP may demonstrate large VF > 20 degrees with V4e and reduced central sensitivity. These RP subjects only detect the V4e in the macula/foveally. Typical RP subjects with advanced degeneration may demonstrate small VF < 20 degrees with V4e, or small VF < 20 with V4e and reduced central sensitivity, with detection of V4e target only in the macula/foveally.

[0101] The subject's visual field may improve in the dosing period as compared to the baseline of the subject's visual field obtained prior to the dosing period. The subject's visual field may continue to improve during the resting period as compared to the improvement in the subject's visual field during the dosing period. The improvement in the subject's visual field observed during the initial dosing period may be sustained at a level above the subject's baseline visual field during the resting period. The improvement in the subject's visual field may improve during the dosing and/or resting period, but return to about baseline by the end of the resting period.

[0102] For RP subjects with *LRAT* or *RPE65* mutation, including without limitation, arRP patients, the subject's visual field may expand by at least 20 degrees, of the baseline retinal area.

[0103] Commencement of a subsequent dosing period may begin upon assessment of the improvement of the subject's visual field during the initial dosing period and during the resting period. For example, the subsequent dosing period may commence if the subject's visual field returns to a level prior to the initial dosing period or to a pre-determined level during the initial resting period. A subsequent dosing period may begin upon assessment of an improvement of <20% from baseline of the subject's visual field after the initial dosing period.

2. Visual Acuity

[0104] Decline in visual acuity (VA) can be noted during the course of RP or other visual disorders associated with an endogenous retinoid deficiency, including LCA. Subjects with early-onset RP have been shown to have more stable VA than other RP types. VA can remain

normal even in individuals with advanced RP with a small island of remaining central VF, although decrease in VA can be also observed in some RP subjects.

[0105] Visual acuity refers to acuteness or clearness of vision, especially form vision, which is dependent on the sharpness of the retinal focus within the eye and the sensitivity of the interpretative faculty of the brain. Visual acuity is a measure of the spatial resolution of the visual processing system and is usually tested in a manner to optimize and standardize the conditions.

[0106] LogMAR charts, particularly the Early Treatment Diabetic Retinopathy Study (ETDRS) charts have become the gold-standard for measuring treatment effects on VA in clinical trials. Protocols are well established such that subjects able to read less than 20 letters at 4 meters are tested at 1 meter. This method measures vision under high contrast and standard room lighting conditions. The Smith-Kettlewell Institute Low Luminance (SKILL) Chart was designed to assess vision under conditions of low contrast that simulates low lighting, through a test performed with standard indoor lighting. The SKILL Chart has a high-contrast near-acuity chart on one side (black letter on white), and a low-luminance, low-contrast chart on the other (gray letters on a dark background). The low reflectance of the dark side of the card simulates testing in a dim environment.

[0107] The degree of improvement in visual acuity over baseline may be dependent on the subject's baseline visual acuity. For patients with very low visual acuity (light perception or hand waving, zero letters), clinically meaningful improvement may be associated with an improvement of 1-5 ETDRS letters. The subject may have a VA improvement of ≥5 ETDRS letters upon administration of a first therapeutic dose. The subject may have a VA improvement of ≥5 to <10 upon administration of a first therapeutic dose. The subject may have a VA improvement of ≥10 to <15 letters upon administration of a first therapeutic dose. The subject may have VA improvements of ≥15 to <20 letters upon administration of a first therapeutic dose. The subject may have VA improvements of ≥20 letters upon administration of a first therapeutic dose. Thus, the subject's visual acuity may improve during the initial dosing period as compared to the subject's visual acuity level prior to the treatment during the initial dosing period, i.e., the subject's visual acuity baseline. The subject's visual acuity may continue to improve during the resting period as compared to the improvement in the subject's visual acuity level observed at the end of the initial dosing period. The improvement in the subject's visual acuity may be sustained above the subject's baseline level during the resting period.

[0108] A subsequent dosing period may begin upon assessment of an improvement of <5 letters from baseline, for subjects with a baseline VA > 0 letters, of the subject's visual acuity after the initial dosing period.

3. Retinal Sensitivity

[0109] A subject's retinal sensitivity can be measured by determining the absolute intensity

threshold, that is, the minimum luminance of a test spot required to produce a visual sensation. Retinal sensitivity is related to the eye's ability to adjust to various levels of darkness and light and to detect contrast.

[0110] Full-field stimulus testing (FST) was developed to measure dark-adapted sensitivity using commercial equipment in patients unable to fixate (Roman, A.J. et al., Physiol. Meas. 28(8):N51-N56 (2007)). The test uses a full-field (Ganzfeld) white-flash stimulus presentation available in a commercial ERG dome (Diagnosys) and available software allows for reliable, efficient psycho-physical measures of absolute threshold, expressed in log luminance (log cd/m2). FST may also be performed using light stimuli delivered with a Colordome Ganzfeld stimulator (Diagnosys LLC, Littleton, MA). In this test method, repeated measurements of sensitivity to a full-field stimulus are obtained in the dark-adapted state with white, red and blue flashes.

[0111] Two color threshold perimetry has been previously described (Lorenz et al., Invest Ophthal Vis Sci. 49(12): 5235-5242 (2008)). To assess the spatial distribution of rod- and cone-mediated function, 2-colour threshold perimetry is performed under scotopic and photopic conditions. A modified Humphrey field analyzer or equivalent may be used. The scoptopic thresholds are measured after dark adaptation. The sensitivity loss may be calculated as the difference between the measured value in the subject and the 10^{th} percentile of normal subjects for each test locus. Photopic thresholds are measured with a background illumination of $10cd/m^2$. Cone sensitivity may be calculated as the difference between the measured value to the long wavelength stimulus and the 10^{th} percentile of normal subjects for each test locus.

[0112] Dark adapted static perimetry measures dark-adapted (including extended dark adaptation of up to 6 hours or longer) threshold sensitivity in subjects, at a range of individual loci throughout the visual field area, which is particularly useful in subjects unable to fixate. The test utilizes the full-field stimulus presentation available in Goldmann perimeter or the commercial ColorDome, which can present flashes as bright as 4.5 log troland-seconds.

[0113] FST has previously been shown to measure rod and cone sensitivity to white, blue, and red stimuli in RPE65-deficient LCA patients who had limited or no ERG responses (Jacobson, S.G. et al., Invest Ophthalmol Vis Sci. 50(5):2368-2375 (2009)). Dark-adapted static perimetry methods may be used to more accurately identify residual vision in the visual field of these subjects. Optimization of retinal sensitivity assessments relevant for subjects with RPE65 gene mutations has been performed previously (Cideciyan, A.V. et al., Proc Natl Acad Sci USA. 105(39): 15112-15117). Thus, , the subject's retinal sensitivity may improve during the initial dosing period as compared to the subject's retinal sensitivity baseline prior to the treatment during the initial dosing period. The subject's retinal sensitivity may continue to improve during the resting period as compared to the improvement in the subject's retinal sensitivity at the end of the initial dosing period. The improvement in the subject's retinal sensitivity may be sustained during the resting period at about the subject's retinal sensitivity level at the end of

the initial dosing period. The improvement in the subject's retinal sensitivity may be sustained at a level above the subject's baseline retinal sensitivity during the resting period.

4. Electroretinograms (ERG)

[0114] ERG testing is a well-accepted standard test and is used routinely to diagnose and monitor progression of most inherited retinal diseases (IRD), including visual disorders associated with an endogenous retinoid deficiency. Physicians specializing in IRD agree that significant, repeatable improvements in ERG responses are indicative of improved visual function. For example, ERG responses are an early indicator of loss of rod and cone function in RP and a decrease in ERG response can be evident within the first few years of life, even though symptoms appear much later. It has been reported that RP patients have decreased or undetectable rod and cone responses, typically with a greater loss of rod than cone ERG responses.

[0115] The three main types of traditional global or full-field ERG that evaluate general retinal response are scotopic (dark adapted, dim flash, rod-mediated ERG), photopic (light adapted, bright flash, con-mediated ERG), and flicker (light adapted, bright flash, 31-Hertz Flicker ERG) testing. Dark adapted, bright flash, rod/cone-mediated ERG may also be evaluated. A limitation of full-field ERG is that the recording is a massed potential from the whole retina. Unless 20% or more of the retina is affected with a diseased state, ERG recordings are usually normal (e.g., a legally blind person with macular degeneration, enlarged blind spot or other central scotomas may have normal global ERGs). Early-onset RP is generally defined as demonstrating an extinguished or markedly reduced ERG response typical of a rod-cone degeneration before the age of 6 years.

[0116] The subject's ERG response may improve during the initial dosing period as compared to the subject's ERG response prior to the treatment during the initial dosing period. The subject's ERG response may continue to improve during the resting period as compared to the improvement in the subject's ERG response observed at the end of the initial dosing period. The improvement in the subject's ERG response may be sustained above the subject's baseline level during the resting period.

5. Dynamic Pupillary Response (Pupillometry)

[0117] Pupillary responses (constriction of the pupil in response to a bright light stimulus) may be abnormal in subjects having a visual disorder as described herein. Dynamic pupillometry is a non-invasive method to record the pupillary response and monitor potential changes in response to treatment. Pupillary reflexes improved in LCA subjects with RPE65 deficiency after receiving gene therapy (Maguire, A.M. et al., New Engl J Med. 358:2240-2248 (2008)). Chromatic pupillometry, in which light stimuli of varying color, intensity, stimulus duration and

time between stimuli, has been established (Park et al., Invest Ophthal Vis Sci. 52(9): 6624-6635 (2011)), with light delivered with a Colordome Ganzfeld stimulator (Diagnosys LLC, Littleton, MA) or equivalent. The examination for rod-weighted recordings and the intrinsic photosensitive retinal ganglion cell recordings are performed after dark adaptation. Video signals of the recordings may be relayed to a processing board that records the pupil diameter in real time into a text file. Relative sustained and transient pupil constriction data are analyzed for clinical significance.

[0118] The subject's pupillary response may improve during the initial dosing period as compared to the subject's pupillary response baseline level prior to the treatment during the initial dosing period. The subject's pupillary response may continue to improve during the resting period as compared to the subject's pupillary response level at the end of the initial dosing period. The improvement in the subject's pupillary response may be sustained during the resting period at about the subject's pupillary response level at the end of the initial dosing period. The improvement in the subject's pupillary response may be sustained at a level above the subject's baseline pupillary response during the resting period.

6. Nystagmus

[0119] Nystagmus is a form of involuntary eye movement that is frequently associated with visual impairment, including LCA. Nystagmus amplitude and frequency is measured non-invasively and can be used to monitor potential changes in response to treatment such as by videotaping the eye movements for qualitative clinical analysis of the subject's oscillation and strabismus. (Maguire, A.M. et al., New Engl J Med. 358:2240-2248 (2008)).

[0120] The subject may demonstrate a decrease in the amplitude and/or frequency of nystagmus during the initial dosing period. The subject may demonstrate a continued decrease in the amplitude and/or frequency of nystagmus during the resting period.

7. *Visual Cortical Function*

[0121] The therapeutic effectiveness of the therapeutic regimens of the disclosure may be monitored using effects of the subject's vision on cortical visual function as measured by functional magnetic resonance imaging (fMRI). Functional scans consist of a contrast sensitivity challenge, movement stimulus challenge, and higher level cognitive challenges. Data are normally displayed as percentage change in MRI signal from baseline. Maps of statistical significance will be displayed on the reconstructed cortical surface from each individual. The pre- and post- treatment scans will be directly compared in terms of the extent and magnitude of activation. Improvement in visual cortical function may be defined based on activation of the visual and/or parietal cerebral cortex.

[0122] Thus, the subject's cortical vision function may improve during the initial dosing period as compared to the subject's cortical vision function baseline level prior to the treatment during the initial dosing period. The subject's cortical vision function may continue to improve during the resting period as compared to the subject's cortical vision function level at the end of the initial dosing period. The improvement in the subject's cortical vision function may be sustained during the resting period at about the subject's cortical vision function level at the end of the initial dosing period. The improvement in the subject's visual cortical function may be defined by activation of the visual cerebral cortex after treatment. The improvement in the subject's visual cortical function is defined by activation of the parietal cortex after treatment.

8. Color Vision

[0123] A color vision test checks a subject's ability to distinguish between different colors. Ishihara plates are used to detect, classify and estimate the degree of defect in color vision. Color vision testing is also used to evaluate the function of the optic nerve and hereditary retinal disease.

[0124] Color vision may be assessed by methods known in the art, including the Ishihara Color Test, Hardy-Rand-Rittler, or Farnsworth-Munsell 100 Hue test. The test consists of a number of colored plates, each of which contains a circle of dots appearing randomized in color and size. Within the pattern are dots which form a number visible to those with normal color vision.

[0125] Thus, the subject's color vision may improve during the initial dosing period as compared to the subject's color vision baseline level prior to the treatment during the initial dosing period. The subject's color vision may continue to improve during resting period as compared to the subject's color vision level at the end of the initial dosing period. The improvement in the subject's color vision may be sustained during the resting period at about the subject's color vision level at the end of the initial dosing period.

9. Dark Adaptation

[0126] Dark adaptation is defined as the recovery of light sensitivity by the retina in the dark after exposure to a bright light. Impairment in dark adaptation rates is associated with a range of visual disease states, and is often an early symptom for RP subjects. Dark adaptation parameters include the time constant of the cone-mediated sensitivity recovery, the time constant of rod-mediated sensitivity recovery, the cone plateau, the rod plateau, the rod-cone break, the rod intercept, the slope and/or time constant of the second component of the rod-mediated recovery, the slope and/or time constant of the third component of the rod-mediated recovery, the transition time between the second and third rod-mediated components, and the duration from the bleaching to the final threshold measurement.

[0127] Methods to measure dark adaptation are known in the art, including those methods defined in US 7,494,222 and US 7,798,646.

[0128] Improvements in the rate of dark adaptation may be determined based on a comparison of a subject's rate of dark adaptation after treatment as compared to the subject's baseline rate. Treatment effects on dark adaptation may also be monitored using subjective, patient reported outcomes, which document improvements in activities of daily living related to the rate of a subject's vision to dark-adapt when transitioning from light to dark environments.

[0129] The subject's rate of dark adaptation may improve during the initial dosing period as compared to the subject's rate of dark adaptation at baseline. The subject's rate of dark adaptation may continue to improve during the resting period as compared to the subject's rate of dark adaptation at the end of the initial dosing period. The improvement in the subject's rate of dark adaptation may be sustained during the resting period at about the subject's rate of dark adaptation at the end of the initial dosing period. The improvement in the subject's rate of dark adaptation may be sustained at a level above the subject's baseline rate of dark adaptation during the resting period.

10. Visual Mobility

[0130] Visual mobility may be used as a measure of improved retinal function. Improvements in visual mobility can be determined by methods known in the art, including standardized obstacle courses and mazes, including those described in Bainbridge et al. N Engl J Med. 358:2231-9 (2008) and Maguire, A.M. et al., New Engl J Med. 358:2240-2248 (2008). Subjects may be assessed based on the time to navigate the course, or based on the number of times a subject bumps into obstacles or walks off course compared to the total number of obstacles present.

[0131] Visual mobility may also be monitored based on subjective, patient reported outcomes. Subjective reports of improvement in mobility may be used to monitor treatment effects through comparison on a subject's reported mobility after treatment and during the resting period, as compared to the subject's reported mobility at baseline.

11. Visual Function Questionnaires

[0132] Questionnaires may be administered to subjects at certain study visits to assess visual function and its effects on activities of daily living. There are a number of known Visual Function Questionnaires (VFQ's) which may be used to assess improvement in a subject's visual function. One such questionnaire is the Children's Visual Function Questionnaire (CVFQ) (see, e.g., Birch, E.E. et al., J. AAPOS. 11:473-9 (2007)). This is a vision-specific quality-of-life instrument designed for use with parents of infants and young children.

[0133] The Low Luminance Questionnaire (LLQ) is a questionnaire that has been developed specifically to assess visual performance of adults in low lighting conditions, such as nighttime or darkened rooms (see, e.g., Owsley, C. et al., Invest Ophthalmol Vis Sci 47:528-535 (2006). This questionnaire was validated in a population of older RP subjects similar to the population eligible for the clinical study described below and correlates to rod-mediated parameters of dark adaptation.

[0134] The Impact of Vision Impairment (IVI) questionnaire and the Impact of Vision Impairment for Children (IVI_C) questionnaire may also be used. These questionnaires were developed and validated to measure the impact of vision impairment on restriction of participation in daily activities in people with low vision.

[0135] The use of the VFQ's assists in identifying subjective improvements in visual function, particularly with respect to activities of daily life following administration of a compound of the disclosure by the therapeutic regimens described herein through comparison of the subject's questionnaire results after treatment and during the resting period as compared to the subject's questionnaire results at baseline.

12. Spectral Domain-Optical Coherence Tomography

[0136] Optical coherence tomography (OCT)/autofluorescence (FAF) machines, such as the Heidelberg Spectralis (Heidelberg Engineering, Germany), may be used to conduct ocular tomography scans. The analyses of the scans may provide information as to the overall retinal health, including visualization of the photoreceptor layer, the outer segments, and measurement of retinal thickness and to assess presence or absence of autofluorescence. Improvement in retinal health may be assessed by comparing a subject's baseline OCT and FAF scans with a subject's OCT and FAF scan after the initial dosing period. A subject's baseline OCT and FAF scans may be correlated to the subject's visual function before and after the initial dosing period.

[0137] The following examples are provided merely as illustrative of various aspects of the disclosure.

Examples

Example 1: Safety Study

[0138] An open-label, repeat dose escalation study of an orally-delivered pharmaceutically acceptable composition of the disclosure was conducted in twenty (20) healthy human volunteers to determine the safety and tolerability of repeat daily oral doses of a composition

comprising 9-cis-retinyl acetate ((2E, 4E, 6Z, 8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl) nona-2,4,6,8-tetraen-1-yl acetate) and butylated hydroxyanisole (BHA) dissolved in soybean oil (USP). The concentration of 9-cis-retinyl acetate in the composition was adjusted such that the volume to be administered was convenient. For the dosing range of the study, compositions of 1.25 mg/mL, 5.0 mg/mL and 20 mg/mL 9-cis-retinyl acetate were prepared, containing 0.10% w/w BHA in Soybean oil (USP). Six dose cohorts of healthy subjects received escalating daily doses of the composition orally from 1.25 mg/m^2 up to 40 mg/m^2, i.e., 1.25, 2.5, 5, 10, 20 and 40 mg/m^2.

[0139] Eighteen subjects received all 7 days of treatment with the study composition, and 2 subjects had missed doses. The mean average age of subjects was 37 years (range (23-59).

[0140] The compositions up to 40 mg/m^2 were found to be well tolerated and there were no serious adverse events after 7 days of monitored therapy in a Phase I testing center. The most frequently reported side effects were headache (6 subjects, 12 events), facial flushing (2 subjects, 7 events), and a facial burning sensation (2 subjects, 6 events), which were primarily reported from the 40 mg/m^2 dose group and collectively accounted for 25 of the 43 (58%) adverse events (AE) reported. In total, 41 of 43 AEs were of mild intensity.

[0141] In some subjects, there was a modest, reversible elevation in triglycerides across all doses and a modest reversible decline in high density lipoproteins (HDL) at the 10 - 40 mg/m^2 doses.

Example 2: Study in RP Patients

Study Protocol

[0142] A study was designed to determine the efficacy of the composition of Example 1 orally administered to human RP subjects having RP caused by mutations in either LRAT or RPE65 (also known as early-onset RP). Seventeen RP subjects received a once-daily dose of the composition orally (40 mg/m^2) for 7 days. Both eyes of each RP subject were evaluated separately. Protocol-defined assessments of visual function included: best-corrected visual acuity testing using Early Treatment Diabetic Retinopathy Study (ETDRS), visual field testing, full-field electroretinogram (ERG); retinal sensitivity (FST), dynamic pupillometry, nystagmus testing, OCT and FAF, and subject questionnaire.

[0143] Baseline visual function tests were performed, within 21 days of Day 0 of the study, including spectral-domain OCT in low light conditions to determine if there were viable photoreceptors in the retina. On Day 0 each RP subject received the first dose of the composition. Treatment was administered on 7 consecutive days (Day 0 to 6, inclusive). RP

subjects had follow-up visits on days 7/8, 14/15, 30, 60 and bimonthly thereafter until retreatment criteria are met. All visual function tests and safety assessments were done on Day 7/8 (24/48 hours after receiving the last dose) as well as on all subsequent visits.

Initial and preliminary Efficacy Assessment for two RP Patients

[0144] The efficacy of the composition of Example 1 was initially tested in two human subjects having RP. The two subjects received a once-daily initial dose of the Composition (40 mg/m2) for 7 days. Subjects were treated on an outpatient basis, but received study treatment in the research clinic under medical supervision for each day of treatment. During the study, subjects were required to limit vigorous physical activity (to avoid laboratory variability) and avoid excessive vitamin A intake in order to reduce the influence of such factors on the assessment of safety variables in this study.

[0145] Both eyes of each subject were evaluated separately. Protocol-defined assessments of visual function included: best-corrected visual acuity testing using Early Treatment Diabetic Retinopathy Study (ETDRS) testing followed by low/high contrast Smith-Kettlewell Institute Low Luminance (SKILL) charts; visual field testing using Goldmann perimetry; full-field electroretinogram (ERG); and full-field stimulus threshold testing (FST). Baseline ERGs, ETDRS, and SKILL tests were repeated twice. During and after treatment, visual function tests were conducted on Day 1, 7, 9/10, and 14/15.

[0146] There was no requirement that the subjects wear eye patch on one or both eyes

[0147] Subject ID 010110 was a 27-year-old male with RP homozygous mutations in the LRAT gene at c.525T>A; p.Ser175Arg. His ETDRS visual acuity at baseline was 71 letters OD and 60 letters OS (approximately 20/40 and 20/62.5 Snellen equivalent) unaided.

[0148] The subject was treated with 40 mg/m^2 of Composition A for 7 days. Small improvements in ETDRS visual acuity were observed, with the highest improvement from baseline of 11.5 letters (OD) at Day 9, and 14.5 letters OS at Month 1.5. Large improvements in GVF OD were detected, and supported by subjective reports of improvements in peripheral vision. Objective testing of cortical visual function before and after drug treatment was tested using fMRI, with marked improvements observed. No changes in cone or rod ERG were seen.

[0149] The subject reported meaningful improvements in activities of daily living. Sensitivity to daylight and fluorescent lights was noted. Dark adaptation times were also improved. The patient was monitored for 1.5 months beyond the end of the treatment period, with improvements from baseline persisting.

[0150] Subject ID 010111 was a 41 year old male with homozygous mutations in the LRAT gene at c.181T>A3; P.TYR61ASP. His ETDRS visual acuity at baseline was 0 letters OD and

1.5 letters OS. The subject was treated with 40 mg/m^2 of Composition A for 7 days. Changes in ETDRS visual acuity were observed in one eye, with the highest improvement from baseline of 24.5 letters (OD) and 0 change (OS) at Day 14.

Interim 30 Day Safety and Efficacy Assessments for 17 RP Patients

[0151] A total of 17 RP subjects ranging in age from 6 to 55 years, mean 29 years with either RPE65 (12 RP subjects) or LRAT (5 RP subjects) mutations were evaluated with baseline VA and GVF values described in Table 1. Both eyes in each RP subject were evaluated independently. Visual Acuity (VA; ETDRS BCVA) ranged from 0-62 letters for the left eye (OS) with a mean of 29.5 letters (~20/250) and ranged from 0-71 letters for the right eye (OD) with a mean of 32.1 letters (~20/200). Visual Field (GVF) ranged from 0.28-2.46 for the left eye with a mean, log retinal area of 1.7 and ranged from 0.48-2.53 for the right eye with a mean, log retinal area of 1.8.

Table 1

Subject	Age	Sex	Race	Gene	VA		GVF log retinal area	
					OD	OS	OD	OS
010110	28	M	Asian	*LRAT*	70.5	59.5	1.62	1.41
010111	41	M	White	*LRAT*	0	1.5	2.47	2.48
010117	6	M	Asian	*LRAT*	37	39.5	2.42	2.40
010118	11	M	Asian	*RPE65*	40.5	19	1.04	0.28
010201	30	M	White	*RPE65*	64	51	2.16	1.93
010202	20	F	White	*LRAT*	60.5	40	1.53	1.40
010301	37	M	Asian	*RPE65*	13.5	22	1.91	1.74
010302	55	F	White	*LRAT*	53	27.5	2.16	2.08
010303	29	M	Asian	*RPE65*	63.5	59	2.31	2.31
010304	36	F	Asian	*RPE65*	11.5	11.5	1.56	1.74
010401	28	F	White	*RPE65*	0	0	0.48	0.42
010402	30	F	White	*RPE65*	39	10.5	1.09	1.77
010403	21	F	White	*RPE65*	23	50	1.39	1.42
010501	40	M	White	*RPE65*	11	3	2.11	1.88
010502	24	F	White	*RPE65*	33	29.5	2.76	1.55
010601	21	M	White	*RPE65*	8	16.5	2.00	2.24
010701	23	M	Hispanic	*RPE65*	17	61.5	1.83	1.73

[0152] At baseline, a total of 13 of the 17 RP subjects reported night blindness with the

majority of RP subjects listing night blindness as the first symptom of RP: 5 RP subjects within the first year of life, 3 RP subjects within 2-4 years of age, 1 RP subject at 17 years of age. Visual field loss was reported in 11 of the 17 RP subjects, while 12 of 17 RP subjects reported visual acuity deterioration.

[0153] GVF analysis was performed on two data sets. Intent to treat (ITT) including all 17 RP subjects, and the Evaluable (per Protocol) set which included RP subjects who fulfilled major inclusion/exclusion criteria. For each RP subject, the two baseline measures were used to identify one VF target which provided a VF log retinal area closest to the midpoint 1.5 log mm^2 of the 0.7 to 2.4 log mm^2 range, to allow for assessment of changes in VF over time. Changes in log retinal area of the selected target size were assessed using a mixed effects model which uses the log retinal area from each eye. Correlation and extent of the correlation between the two eyes of the same RP subject were accounted for in the analysis. GVF responders were defined as eyes with at least 20% improvement in VF compared to their baseline measure.

[0154] Three distinct visual field patterns were observed across the 17 RP subjects in this study. 1. Typical RP, less advanced (9 RP subjects) demonstrated VF > 20 degrees detectable with the V4e target. This pattern was similar to VF baselines for LCA subjects. Mean age was 20.9 years (range 6-30 years). 2. Atypical RP (3 RP subjects, same RPE65 mutations - c,179;pLeu60Pro homo): large VF > 20 degrees with V4e and reduced central sensitivity. These RP subjects could only detect the V4e in the macula/foveally. Mean age was 34.5 years (range 29-37 years). 3. Typical RP/Advanced degeneration: small VF < 20 degrees with V4e, or small Vf < 20 with V4e and reduced central sensitivity, only detecting the V4e target in macula/foveally. Mean age was 39.2 years (range 28-55 years).

[0155] Figure 2 summarizes the proportion of GVF responders to treatment in both the ITT and per Protocol sets. Dependent on the isopter selected for analysis, the proportion of responders in the ITT group was 44.1-50% at Day 7, 38.2-44.1% at Day 14, and 35.5-41.9% at Day 30. The proportion of responders in the evaluable (per protocol) subset, also dependent on the isopter selected for analysis, was 51.7-60.7% at Day 7, 44.8-53.6% at Day 14, and 34.6-40% at Day 30. When these sets were further separated based on VF severity at baseline, a higher percentage of responders were found in the least severe subgroup, both in the ITT and per protocol sets (Figure 3, all subjects included, and Figure 4, 3 subjects excluded). After 7 days of dosing, the average GVF areas from baseline showed statistically significant improvements of 34% at day 7 (p=0.005), 29% at day 14 (p=0.02) and trended towards a statistically significant improvement of 23% at day 30 (p=0.07) in the evaluable (per protocol) RP subjects (n=14). In the ITT set (n=17), average GVF area from baseline improved by 22% at day 7 (p=0.03, statistically significant), 16% at day 14 (p=0.13) and 18% at day 30 (p=0.096) (Figure 5). Figure 6 shows the percent of GVF responders to treatment in the ITT set wherein a responder is defined as patients/eyes for whom retinal area, relative to the mean baseline value, increased by at least 20% on 2 consecutive follow-up visits until month 1.

[0156] Nine of 17 RP subjects (53%) showed an improvement in BCVA over baseline in at least one eye by greater than or equal to 5 ETDRS letters. The VA response was further separated

by demographics to evaluate subpopulations which may be more sensitive to the treatment, as shown in Table 2. At day 7, 27% of eyes had a VA improvement of ≥5 ETDRS letters, with 15% of eyes improving by ≥5 to <10 and 12% of eyes improving by ≥10 to <15 letters. At Day 14, 37% of eyes had a VA improvement of ≥5 ETDRS letters, with 28% of eyes improving by ≥5 to <10 and 6% of eyes improving by ≥10 to <15 letters, and 3% of eyes improving by ≥20 letters. At day 30, 34% of eyes had a VA improvement of ≥5 ETDRS letters, with 19% of eyes improving by ≥5 to <10 and 15% of eyes improving by ≥10 to <15 letters. When evaluated based on gene mutation, for the 5 RP subjects with LRAT mutations, 40% of eyes improved by ≥5 at day 7, 60% at day 14, and 50% at day 30. For the 12 RP subjects with RPE65 mutations, 21% of eyes improved by ≥5 at day 7, 23% at day 14, and 30% at day 30. Figure 7 shows the mean VA change from baseline, ETDRS letter score improvement. At Day 7, Day 14 and Month 1, mean VA improvement for all subjects (ITT group) was found to be 3 +/-1 letters, 3.9 +/- 0.9 letters, and 3.2 +/- 1.2 letters respectively. The evaluable subset, defined as excluding one eye of one subject and both eyes of another subject, all having baseline VA of zero letters, had mean VA improvement of 3.5 +/-1.2 letters, 4.8 +/- 1.5 letters, and 3.3 +/- 1.3 letters respectively.

Table 2: VA Response* by Baseline Value

Response by age	No. of eyes	%
<20 years	2/4	50%
≥20 years	9/30	30%
Response by gender		
Male	9/20	45%
Female	2/14	14%
Response by race		
White	5/20	25%
Asian	5/12	42%
Other	1/2	50%
Response by Gene deficiency		
LRAT	6/10	60%
RPE65	5/24	21%
*VA change from baseline ≥5 letters for 2 consecutive visits between day 7 and month 1.		

[0157] Figure 8A shows the proportion of VA responders in the ITT set when responder is defined as an improvement of greater than or equal to 5 letters from baseline with the exception that if baseline is zero, a responder is defined as anything above baseline. Figure 8B shows the proportion of VA responders when the evaluable subset excludes eyes with baseline of zero (i.e., such that one eye of one subject and both eyes of another subject are excluded for having a baseline VA=0). Figure 9 shows the percentage of VA responders in the ITT set

when responder is defined as an improvement of greater than or equal to 5 letters from baseline with the exception that if baseline is zero, a responder is defined as anything above baseline, for two consecutive visits until one month.

[0158] Baseline visual functions showed a broad range of severely reduced baseline BCVA (0-65 letters) and VF (6-75 degrees) consistent with severe retinal degeneration. In small subsets of RP subjects, the effects of treatment on several parameters of light sensitivity in dim light (night vision), pupillary reflexes, and responses of the visual cortex to potential changes in visual stimuli (functional magnetic resonance imaging, fMRI) were measured.

[0159] An fMRI substudy (n=2) of the present study showed activation of several previously quiet areas of the visual and parietal cerebral cortex after treatment, e.g., as measured at day 11.

[0160] Several RP subjects across the study self-reported a gain in night vision.

[0161] Safety assessments were performed on all RP subjects to provide baseline (pretreatment) and postdose measures. Vital signs were evaluated at screening, on Day -1, predose and 4 hours postdose on treatment days. Triplicate ECG recordings and clinical laboratory tests were performed at screening, on Day -1, and on days 3 and 7. Safety assessments were also done on Day 14/15 and each subsequent visit if the RP subject had ongoing, clinically significant abnormal results at the preceding visit. The clinical laboratory tests performed included hematology, serum chemistry (including total cholesterol, triglycerides, HDL, and LDL), and urinalysis. Analysis of the safety profile indicated that the study treatment was well tolerated, with safety results consistent with the results in healthy adult volunteers (See Example 1). Effects on lipid metabolism, a recognized class effect for retinoids, were observed. Clinically significant laboratory results largely returned to baseline through the resting period. Other adverse events included mild to moderate headache which resolved by the end of the 7-day treatment period for most subjects, nausea which resolved in one day, and photophobia.

[0162] Preliminary results in RP subjects with early-onset RP due to mutations in *LRAT* and *RPE65* show a rapid and significant improvement in certain visual function parameters after a 7 day course of treatment with an acceptable safety profile.

Example 3: Safety and Efficacy Study for LCA Subjects

[0163] The study of Example 2 was also designed to determine the efficacy of the composition of Example 1 orally administered to human subjects having LCA (caused by mutations of either LRAT or RPE65). Subjects received a once-daily loading dose of the composition orally (40 mg/m^2) for 7 days. Subjects were treated on an outpatient basis, but they received study treatment in the research clinic under medical supervision for each day of treatment. Both eyes

of each subject were evaluated separately. Protocol-defined assessments of visual function included: best-corrected visual acuity testing using Early Treatment Diabetic Retinopathy Study (ETDRS) testing followed by low/high contrast Smith-Kettlewell Institute Low Luminance (SKILL) charts; visual field testing using Goldmann perimetry; full-field electroretinogram (ERG); and full-field stimulus threshold testing (FST). Baseline ERGs, ETDRS, and SKILL tests were repeated twice. During and after treatment, visual function tests were conducted on Day 1, 7, 9/10, and 14/15.

Summary of Preliminary Efficacy Data in 9 LCA Patients as well as two RP Patients of Example 2

[0164] A total of 11 subjects were studied, comprising two mutation types (LRAT and RPE65), two disease types (LCA and RP), different age ranges (6 subjects 6-15 years and 5 subjects 21-41 years), and a broad range of baseline visual function, as shown in Table 3. Four distinct ranges of baseline VA were established: hand motion and light perception, VA in the 0-20 letter range, VA in the 20-50 letter range, and VA in the 50-70 letter range. Largest responses in improvement in VA was observed for patients with a modest level of retinal function (VAs in the 20-40 letter range), all of which were treated with 40 mg/m^2 of the Composition (Figure 10). The best responses, 3 lines of improvement, were seen in the younger patients (10-13 years). Relative improvements in visual acuity over baseline for the 11 subjects were monitored for up to 14 months post dosing, demonstrating persistence of clinically meaningful improvements (Figure 11).

Table 3

Subject	Type	Age	Sex	Race	Dose (mg/m^2)	Base line VA (ltrs)	Best Change from Baseline	Visit
1 LCA	*LRAT*	10	F	White	40	OD 36	OD 51 (+15)	Day 8
	HOMOZYGOUS C.217_218DELAT, P.MET73ASPFSX47					OS 26	OS 51 (+25)	Month 4
2 LCA	*LRAT*	12	M	White	40	OD 9	OD 18 (+9)	Month 6.5
	HOMOZYGOUS C.217_218DELAT, P.MET73ASPFSX47					OS 7	OS 25 (+18)	Day 9
3 LCA	*LRAT*	38	F	White	40	OD 0	OD 5 (+5)	Month 6
	HOMOZYGOUS C.217_218DELAT, P.MET73ASPFSX47					OS 0	OD 3 (+3)	Month 2.5
4 LCA	*RPE65*	31	M	Indian	40	OD 0	OD 1 (+1)	Month 2.5
	p.W331X (TGG>TAG) c.992G>A					OS	OS 21 (+6)	Day 14

Subject	Type	Age	Sex	Race	Dose (mg/m^2)	Base line VA (ltrs)	Best Change from Baseline	Visit
						15		
5 LCA	*RPE65*	13	F	Asian	40	OD 31	OD 67 (+36)	Month 4
	Leu67Arg CTG>CGG heterozygous - EPP=3					OS 34	OS 63 (+29)	Day 14
6 LCA	*RPE65*	6	F	Asian	40	OD 64	OD 70 (+6)	Day 14
	Leu67Arg CTG>CGG heterozygous - EPP=3					OS 61	OS 68 (+7)	
7 LCA	*RPE65*	21	F	Syrian	40	OD 60	OS 60 (0)	Day 14
	-/-V19DEL2BP, NT 57+58					OS 52	OS 55 (+3)	Day 9
8 LCA	*RPE65*	15	F	Brazilian	10	OD 28	OD 32 (+4)	Day 9
	EXON 4 272>A R91Q GA/CT EXON 10 1022T>C L341S TC/AG					OS 25	OS 27 (+2)	
9 LCA	*RPE65*	14	F	Hispanic	10	OD 37	OD 51 (+14)	Day 14
	EXON 4 272G, EXON 10 1022T					OS 47	OD 46 (-1)	
10 RP	*LRAT*	28	M	Indian	40	OD 71	OD 82 (+11.5)	Day 9
	HOMOZYGOUS EXON 2 C.525T>A; P.SER175ARG					OS 60	OS 74 (+14.5)	Month 1.5
11 RP	*LRAT*	41	M	White	40	OD 0	No change	Day 14
	HOMOZYGOUS EXON 2 C.181T>A3 P.TYR61ASP					OS 1.5	OD 26 (+24.5)	

[0165] AMA low vision grid analyses of the GVFs from Day 14 for the first 9 patients treated showed that 7 of 9 patients demonstrated marked improvements as detected with either the smaller I4e target (Figure 12) or the larger V4e target (Figure 13).

[0166] Preliminary data obtained from use of the Children's Visual Function Questionnaire (CVFQ) or Low Luminance Questionnaire (LLQ) have been combined with subjective reports on improvements in activities of daily living, and support the rapid improvement in visual function and prolonged therapeutic benefit of treatment with the Composition.

[0167] The study treatment was well tolerated. Adverse events related to treatment included transient photophobia and headaches, vomiting, moderate elevations in triglyceride levels, and a trend toward a decrease in HDL levels in all subjects. Effects on lipid metabolism, a recognized class effect for retinoids, was found to peak at Day 7 of dosing, but returned to baseline within 4 weeks after treatment was completed, as shown in Tables 4-7. Overall, adverse events, including effects on lipid metabolism, were more pronounced in the 40 mg/m2 group relative to the lower dosed 10 mg/m2 group.

Table 4: Triglycerides

	10 mg/m2 (n=2)	40 mg/m2 (n=9)	Total (n=11)
Baseline	0.3 ± 0.0	1.0 ± 0.5	0.9 ± 0.5
Day 3	0.5 ± 0.3	1.5 ± 0.7	1.3 ± 0.8
% change	57.1%	55.8%	56.0%
Day 7	0.6 ± 0.2	2.0 ± 0.8	1.7 ± 1.0
% change	66.1%	113.4%	103.9%
Day 9	0.4	1.6 ± 0.6	1.5 ± 0.8
% change	17.6%	82.2%	73.0%
Day 14	-	1.2 ± 0.5	1.2 ± 0.5
% change	-	12.0%	12.0%

Table 5: HDL

	10 mg/m2 (n=2)	40 mg/m2 (n=9)	Total (n=11)
Baseline	1.3 ± 0.1	1.1 ± 0.2	1.1 ± 0.2
Day 3	1.2 ± 0.2	0.9 ± 0.2	1.0 ± 0.2
% change	-6.3%	-16.2%	-13.7%
Day 7	1.2 ± 0.2	0.8 ± 0.1	0.9 ± 0.2
% change	-2.5%	-20.1%	-16.6%
Day 9	1.3	1.0 ± 0.1	1.0± 0.2
% change	-2.9%	-5.6%	-5.0%
Day 14	-	1.1 ± 0.2	1.1 ± 0.2
% change	-	5.8%	5.8%

Table 6: Cholesterol

	10 mg/m2 (n=2)	40 mg/m2 (n=9)	Total (n=11)
Baseline	4.3 ± 0.0	4.0 ± 0.7	4.1 ± 0.7
Day 3	4.3 ± 0.2	3.8 ± 0.6	3.9 ± 0.6
% change	-1.2%	-1.3%	-1.3%
Day 7	4.5 ± 0.3	4.3 ± 0.6	4.3 ± 0.6
% change	3.4%	11.6%	9.9%
Day 9	4.5	4.5 ± 0.8	4.5 ± 0.7

	10 mg/m2 (n=2)	40 mg/m2 (n=9)	Total (n=11)
% change	2.8%	23.2%	20.3%
Day 14	-	4.7 ± 0.6	4.7 ± 0.6
% change	-	18.1%	18.1%

Table 7: LDL

	10 mg/m2 (n=2)	40 mg/m2 (n=9)	Total (n=11)
Baseline	2.9 ± 0.1	2.5 ± 0.7	2.6 ± 0.6
Day 3	2.8 ± 0.3	2.3 ± 0.4	2.4 ± 0.5
% change	-2.4%	-0.1%	-0.6%
Day 7	3.0 ± 0.3	2.6 ± 0.7	2.7 ± 0.6
% change	2.2%	10.3%	8.7%
Day 9	2.9	3.0 ± 0.7	3.0 ± 0.6
% change	4.6%	31.3%	26.0%
Day 14	-	3.0 ± 0.6	3.0 ± 0.6
% change	-	26.0%	26.0%

Example 4: Final Efficacy Assessments in RP and LCA subjects, including those of Examples 2 and 3

[0168] A total of 32 subjects were enrolled in the study overall: 14 LCA subjects and 18 RP subjects. All LCA and RP subjects completed the 7-day treatment period. All LCA subjects had at least 6 months of follow-up, with 12 LCA subjects (86%) having at least 12 months of follow-up, and 2 LCA subjects (17%) having at least 2 years of follow-up. The follow-up period for RP subjects tended to be shorter than that of LCA subjects because RP subjects tended to enter the study later and had the option of entering the retreatment study (Example 6 below) before they reached the 12-month time point. All RP subjects had at least 2 months of follow-up, and 13 subjects (72%) had 8 months of follow-up. There were no visits for RP subjects beyond Month 8.

[0169] The overall study population had a mean age of 23.9 years (range 6-55) and the majority was female (56%) and Caucasian (56%). LCA subjects were younger on average than RP subjects, with a mean age of 18 years (range 6-38 years) vs 28 years (range 6-55 years) for RP subjects. Nine of 14 LCA subjects were under 18 years, compared to 2 of 18 RP subjects.

[0170] The LCA population was predominantly female (71%), whereas the RP population was more balanced (44% female). The racial composition of the two populations was similar, with the LCA population being 50% Caucasian, 21% Asian, 21% Hispanic and 7% other (Syrian),

while the RP population was 61% Caucasian, 33% Asian, and 6% Hispanic.

[0171] In the overall study population 20 subjects (63%) had a deficiency in RPE65 compared to 12 subjects (38%) with a deficiency in LRAT. The LCA population had an equal number of subjects with each gene mutation, while the RP population had a higher incidence of RPE65 deficiency (13 subjects, 72%). The two LCA subjects who received the 10 mg/m2 dose were both female, Hispanic teenagers with RPE65 deficiency.

[0172] The 14 LCA subjects ranged in age from 6 to 38 years, mean 17.9 years with either RPE65 (7 subjects) or LRAT (7 subjects) mutations were evaluated with VA and GVF levels at baseline. Visual Acuity (VA; ETDRS BCVA) ranged from 0-68 letters for the left eye (OS) with a mean of 30.3 letters (~20/250) and ranged from 0-64 letters for the right eye (OD) with a mean of 30.3 letters (~20/250). Visual Field (GVF) for the optimized primary isopter selected for each subject ranged from 0.62-2.81 for the left eye with a mean, log retinal area of 2.0 and ranged from 0.68-2.83 for the right eye with a mean, log retinal area of 2.0.

[0173] The 18 RP subjects ranged in age from 6 to 55 years, mean 28.5 years with either RPE65 (13 RP subjects) or LRAT (5 RP subjects) mutations were evaluated with VA and GVF results described in Figure 2. Both eyes in each RP subject were evaluated independently. Visual Acuity (VA; ETDRS BCVA) ranged from 0-62 letters for the left eye (OS) with a mean of 30.4 letters (~20/250) and ranged from 0-71 letters for the right eye (OD) with a mean of 30.4 letters (~20/250). Visual Field (GVF) for the optimized primary isopter selected for each subject ranged from 0.40-2.53 for the left eye with a mean, log retinal area of 1.8 and ranged from 0.48-2.53 for the right eye with a mean, log retinal area of 1.8.

[0174] In the ITT analysis, including all LCA and RP subjects, a substantial majority of LCA subjects (10 of 14, 71%) had an increase in retinal area of at least 20% in at least 1 eye, with a mean duration of response of 269 days (range 5-801 days). Seven LCA subjects (50%) had an increase in retinal area of at least 40% in both eyes, with a mean duration of response of 275 days (range 7-801 days). RPE65-deficient LCA subjects were more likely to respond than LRAT-deficient LCA subjects, but the duration of response was similar for the 2 mutations.

[0175] For RP subjects, 8 of 18 subjects (44%) had an increase in retinal area of at least 20% in at least 1 eye, with a mean duration of response of 72 days (range 7-253 days) and 2 subjects (11%) had an increase in retinal area of at least 40% in both eyes, with a mean duration of response of 80 days (range 16-174 days). The response rates were similar for the two gene mutations, but the duration of response was substantially longer in LRAT-deficient eyes than RPE65-deficient eyes (123 vs. 49 days of at least 20% response for LRAT- and RPE65-deficient eyes, respectively, and 104 vs. 67 days of at least 40% response for LRAT- and RPE65-deficient eyes, respectively).

[0176] A post hoc analysis was performed to determine the time to initiation of a GVF response occurring within 6 months of treatment. The median time to initiation of a GVF response was 7 days for a response of at least 20%, and 9 days for a response of at least

40%.

[0177] Twelve 12 RP subjects (67%) had a VA increase of at least 5 letters from baseline in at least 1 eye, and 1 RP subject (6%) had an increase of at least 10 letters in both eyes. In comparison, 6 LCA subjects (43%) had a VA increase of at least 5 letters from baseline in at least 1 eye, and 3 LCA subjects (25%) had an increase of at least 10 letters in both eyes. The mean duration of both the ≥5 letter and ≥10 letter VA responses was higher in LCA eyes (313 and 316 days, respectively, with a range of 5-801 days for both ≥5 letter and ≥10 letter responses) than in RP eyes (125 days (range 13-246 days) and 112 days (range 13-206 days), respectively). VA response rates were higher for LRAT-deficient RP subjects than RPE65-deficient RP subjects. The median time to initiation of a visual acuity response was 8 days for a response of at least 5 letters, and 7 days for a response of at least 10 letters.

[0178] The 2 LCA subjects who received 10 mg/m^2 QLT091001 had increases in GVF retinal area of at least 40% in both eyes; however, neither of these subjects had a VA response.

[0179] The mean and median change from baseline stayed positive throughout the study. The VA mean change from baseline in LCA subjects was quite variable over time, ranging between 0.5 and 6.6 letters. The median change from baseline was more consistent, particularly after the Month 2 visit when they ranged from 2 to 3 letters. In RP subjects the mean VA change brome baseline ranged from 3 to 4 letters from the Day 14 visit onward, and the median ranged from 1 to 3.5 letters; both the mean and median showed a slight downward trend over time (Figure 14).

[0180] The results of the evaluable analysis, which included subjects who fulfilled major inclusion/exclusion criteria, were generally similar to the ITT analysis.

[0181] Other efficacy assessments (including full-field ERG, full-field sensitivity and color vision) were performed on some subjects, however there was not enough data to draw conclusions for the study population.

[0182] Selective plasma concentration monitoring was done during the study for 2 LCA subjects who received daily 10 mg/m^2 daily doses of the treatment, 6 LCA subjects and 18 RP subjects who received 40 mg/m^2 daily doses of the treatment over 7 days. Pharmacokinetic analyses showed the predominant metabolites to be either 9-*cis*-retinyl oleate or 9-*cis*-retinyl palmitate and 13,14-dihydro-9-*cis*-retinoic acid. At 4 hours after dosing, the concentration of these compounds was higher than that of 9-cis-retinyl acetate and 9-*cis*-retinol.

[0183] The results of the children's vision-related quality of life questionnaire did not show consistent improvements after treatment; however interpretation of the results is difficult due to the small number of respondents. The LLQ administered to adults showed increases in the mean score for all of the visual function subcategories for LCA subjects. For RP subjects there were variations but no consistent trends for the visual function subcategories except for

extreme lighting, for which there was a slight decrease in ability over the course of the study.

[0184] Baseline SD-OCT (Spectralis HRA+OCT) parameters were compared to baseline visual function; baseline SD-OCT and changes were compared to the visual field response to treatment. The average thickness of the outer segment (OS) layer (measured from the outer segment/retinal pigment epithelium border to the inner segment ellipsoid band) was calculated with a computer program aided by manual segmentation.

[0185] Thirty-nine of 62 eyes had VA of ≥20 letters (20/400 or better) at baseline. Of these, 36 (92%) had readily detectable OS (>10 µm in thickness) in the fovea. Eighteen of 28 eyes (64%) with LCA and 15/34 eyes (44%) with RP responded to treatment (increase in GVF retinal area of ≥20% at two consecutive study visits). Among these responders, the average baseline thickness of the OS layer (central 20°) was 14.22 µm (reduced by 56% from normal average [32 µm]) in the LCA cohort and 8.63 µm (reduced by 73% from normal) in the RP cohort. Non-responders had average baseline OS thickness of less than 5.72 µm in both cohorts (reduced by >82% from normal). The reductions of OS thickness in central 20° were significantly higher in non-responders than responders in the LCA cohort (p=0.003), but not significantly different in the RP cohort (p=0.27). The OS thickness in the central 20° measured at baseline did not change significantly during the follow-up visits.

[0186] Treatment with up to 40 mg/m^2 for 7 days was well tolerated. All subjects enrolled in the study experienced at least one adverse event (AE) related to treatment. The most common associated AE was headache (88% of subjects), followed by photophobia (50%), and blood triglycerides increased (31%). Treatment resulted in short term deviations from normal in a number of laboratory parameters in a minority of subjects. Most of these parameters had returned to normal in all affected subjects by Day 14 or Month 1. Cholesterol and TGs returned to normal by Month 2 and hematocrit returned to normal by Month 4.

Example 5: Safety Study of Multiple-Dose Administration

[0187] A randomized, open-label, placebo-controlled, parallel-design, multiple-dose study was designed to investigate the safety, tolerability and pharmacokinetics of multiple-dose oral administration of the composition of Example 1 in healthy human volunteers. 35 subjects were enrolled. The study consisted of subjects receiving 4 (placebo and 20 mg/m^2 groups) or 6 (40 and 60 mg/m^2 groups) consecutive 28-day dosing/washout cycles (7-day dosing and 21-day washout). After the final cycle, subjects were followed up for 2 months. During each cycle, subjects received either a therapeutic dose comprising a once-daily dose of the compositions of Example 1 orally (9-cis-retinyl acetate and 0.1% butylated hydroxyanisole (BHA) in soybean oil) (USP) administered at 20 mg/m^2, 40 mg/m^2, 60 mg/m^2) or placebo for 7 days, followed by a 21 day resting period during which the subjects did not receive treatment. Subjects were periodically monitored during the cycle for various adverse events, such as headaches, facial flushing and facial burning sensation. Subjects were also monitored for toxicity associated with

treatment such as an elevation in triglycerides and decline in high density lipoproteins (HDL). Adverse events observed included headache, photophobia, nausea, ALT increase, elevated triglycerides, and elevated AST.

[0188] No new or unexpected adverse events were observed in the study. Up to six repeat treatment cycles with the compositions of Example 1 at doses of 20 mg/m$^{2/}$day, 40 mg/m$^{2/}$day, and 60 mg/m$^{2/}$day for seven days followed by a 21 day washout period was generally safe and well tolerated. The safety profile of repeated treatment cycles was similar to that of one treatment cycle, with an overall trend toward reduction in the severity of the Adverse Events with each subsequent dosing cycle. The safety results of this study further support the use of repeat dosing of pharmaceutical compositions of 9- or 11-cis retinyl esters, including the oral composition of Example 1, in intermittent dosing cycles in subjects with RP.

[0189] Interim Pharmacokinetic results of the study were derived from plasma concentrations of 9-cis-retinyl acetate and its metabolites, measured throughout the study period at prescribed time points. The scope of this interim PK analysis encompasses samples from Cohort 1 including the placebo (n=2), 40 mg/m^2 (n=6) and 60 mg/m^2 (n=2) dose groups obtained in treatment cycles 1, 2 and 3.

[0190] The plasma samples were analyzed by liquid chromatography-mass spectrometry-mass spectrometry (LC/MS/MS) for parent drug and potential metabolites. Noncompartmental (NCA) pharmacokinetic (PK) parameters such as AUC were obtained using the WinNonlin software with observational determination of C_{max}, t_{max}, and duration of concentrations above baseline (TD).

[0191] 9-cis-Retinyl acetate plasma concentrations were low and transient, indicative of rapid first-pass metabolism, with further metabolism to non-polar and polar metabolites. At 40 mg/m^2, administered in repeated seven day cycles, the 9-cis-retinol and retinyl ester metabolites showed slight to modest accumulation on multiple-dosing with higher AUC values on Day 7 in accordance with expectations from Day 1. The longer persisting metabolites had rising daily C_{min} values consistent with modest accumulation and these patterns and concentrations were similar for Cycles 1, 2, and 3 with no accumulation being observed from cycle to cycle

Example 6: Effects of Repeated Treatments on Safety and Vision Outcome in Subjects with inherited deficiencies of RPE65 or LRAT

[0192] This study is designed to investigate the effects of repeated treatments on the safety and efficacy of up to three additional courses of the composition of Example 1 orally administered once daily for 7 days to human subjects with LCA or RP due to inherited deficiencies in RPE65 or LRAT. The study was also designed to evaluate whether the up to 3

additional courses of treatment can maintain or improve visual function in these subjects.

[0193] The study will enroll up to approximately 28 subjects with LCA or RP due to RPE65 or LRAT deficiency. Subjects with LCA are 5-65 years of age (inclusive), and subjects with RP are 18-65 years of age (inclusive). All subjects will have previously received a 7-day treatment course and completed the Day 30 visit according to the study protocol of Example 2. Subjects will meet one of the following criteria at least 1 month after the start of the 7-day treatment course of Example 2: a) Follow-up GVF increased ≤20% from baseline in at least 1 eye; or, b) Follow-up GVF decreased below the highest previous response by >20%; or, c) considered a reasonable candidate for retreatment based on regression or lack of response in other parameters of visual function, but who do not meet the other (GVF) criteria.

[0194] For each treatment course, subjects will receive an oral dose of the composition of Example 1 once daily for 7 days. The oral dose will be: 40 mg/m^2 for subjects whose follow-up GVF in at least 1 eye, at least 1 month after the start of the 7-day treatment course does not increase (i.e., increases ≤20% from baseline) (subjects previously treated with a 10 mg/m^2 dose), or, decreases below the highest previous response by >20% (subjects originally treated with 10 or 40 mg/m^2); 60 mg/m^2 for subjects whose follow-up GVF in at least 1 eye, at least 1 month after the start of the 7-day treatment course does not increase (i.e., increases ≤20% from baseline) (subjects originally treated with 40 mg/m^2); or, 40 or 60 mg/m^2, for subjects considered reasonable candidates for retreatment.

[0195] Subjects will receive up to 3 courses of study treatment. A minimum of 3 weeks is required between the last day of the previous treatment course and the first day of the next treatment course. At Day 30 (±3 days) after the start of the first and second treatment courses, safety and vision outcome data will be evaluated for retreatment decisions. A subject will receive the second treatment course (once daily dose of the composition of Example 1 for 7 days), with a dose of 40 or 60 mg/m^2, if there are no safety concerns and: follow-up GVF in at least 1 eye does not increase (i.e., increases ≤20% from the study baseline), or follow-up GVF in at least 1 eye decreases below the highest previous response by >20% after the first course of treatment in this study, or the subject does not meet the GVF criteria but is considered as a reasonable candidate for retreatment based on (1) regression or lack of response in other parameters of visual function (e.g., subjective reports of changes in color vision or adaptation to low light), or (2) the potential for further improvement in GVF if GVF response was sustained.

[0196] A subject will receive the third treatment course (once daily dose of the composition of Example 1 for 7 days), with a dose of 40 or 60 mg/m^2, if there are no safety concerns and: follow-up GVF in at least 1 eye decreases below the highest previous response by >20% after the second course of treatment, or the subject does not meet the GVF criteria but is considered as a reasonable candidate for retreatment based on (1) regression or lack of response in other parameters of visual function (e.g., subjective reports of changes in color vision or adaptation to low light), or (2) the potential for further improvement in GVF if GVF

response is sustained.

[0197] Subjects who are not retreated based on the retreatment criteria evaluated at Day 30 (±3 days) will continue to be followed up. Such subjects may start the next treatment course at any subsequent follow-up visit up to Month 12 of the previous treatment course if there are no safety concerns and the subject meets the retreatment criteria as specified for Treatment Course 2 or Treatment Course 3.

[0198] Baseline visual function tests will be performed. One Day 0, each subject will receive the first dose of the composition of Example 1. Treatment will be administered for 7 consecutive days (Day 0 to Day 6, inclusive). Blood samples for the study drug and metabolite analysis will be collected for the first and last doses (i.e., 4 hours postdose on Days 0 and 6 and before breakfast on Days 1 and 7). Subjects will have follow-up visits on Days 7/8, 14/15 and 30; and Months 2, 4, 6, 8, 10, and 12 for each treatment course, or up to the start of the next treatment course. Protocol-defined assessments of visual function will include: best-corrected visual acuity testing using ETDRS, visual field testing, full-field electroretinogram (ERG), retinal sensitivity (FST), dynamic pupillometry, nystagmus testing, OCT, FAF, and subject questionnaire.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Syntetisk retinalderivat til anvendelse til forbedring af synsfunktionen hos et individ med en endogen retinoiddeficiens ved hjælp af en fremgangsmåde, som omfatter:
a. administrering af en første terapeutisk dosis af et syntetisk retinalderivat, hvor det syntetiske retinalderivat er 11-cis-retinylacetat, 9-cis-retinylacetat eller 9-cis-retinylsuccinat, hvor den første terapeutiske dosis administreres som en delt dosis over et tidsrum på fra 2 til 7 dage;
b. tilvejebringelse af en hvileperiode på 14 dage, 15 dage, 16 dage, 17 dage, 18 dage, 19 dage, 20 dage, 21 dage, 22 dage, 23 dage, 24 dage, 25 dage, 26 dage eller 27 dage; og
c. administrering af en anden terapeutisk dosis af det syntetiske retinalderivat til individet efter endt hvileperiode, hvor den endogene retinoiddeficiens er retinitis pigmentosa (RP) eller Lebers kongenitale amaurose (LCA).

2. Syntetisk retinalderivat til anvendelse ifølge krav 1, hvor individet har:
(a) RP;
(b) tidligt debuterende eller juvenil RP;
(c) LCA; eller
(d) en mutation i et gen valgt blandt LRAT- eller RPE65-genet.

3. Syntetisk retinalderivat til anvendelse ifølge krav 1 eller 2, hvor fremgangsmåden yderligere omfatter gentagelse af trinene b og c en eller flere gange.

4. Syntetisk retinalderivat til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor den første terapeutiske dosis administreres:
(a) som en delt dosis over et tidsrum på 7 dage;
(b) som en delt dosis over et tidsrum på 5 dage; eller
(c) som en delt dosis over et tidsrum på 6 dage, 4 dage, 3 dage eller 2 dage.

5. Syntetisk retinalderivat til anvendelse ifølge et hvilket

som helst af kravene 1-4, hvor hvileperioden er valgt blandt:
(a) et interval på 21 dage;
(b) et interval på 14 dage.

6. Syntetisk retinalderivat til anvendelse ifølge et hvilket som helst af kravene 1-5, hvor individet er et menneske.

7. Syntetisk retinalderivat til anvendelse ifølge krav 6, hvor mennesket er en person med RP, hvor personen med RP er 15 år eller ældre, 20 år eller ældre, 30 år eller ældre, 40 år eller ældre, 50 år eller ældre eller 60 år eller ældre, når det terapeutiske program påbegyndes.

8. Syntetisk retinalderivat til anvendelse ifølge krav 6, hvor mennesket er en person med RP, hvor personen er 50 år eller yngre, når det terapeutiske program påbegyndes.

9. Syntetisk retinalderivat til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor det syntetiske retinalderivat er 9-cis-retinylacetat.

10. Syntetisk retinalderivat til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den første terapeutiske dosis:
(a) er fra 280 mg/m^2 til 420 mg/m^2;
(b) er 280 mg/m^2;
(c) er 420 mg/m^2;
(d) er 10 mg/m^2 pr. dag;
(e) er 20 mg/m^2 pr. dag;
(f) er 40 mg/m^2 pr. dag; eller
(g) er 60 mg/m^2 pr. dag.

11. Syntetisk retinalderivat til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor retinalderivatet er til anvendelse til oral administration.

DRAWINGS

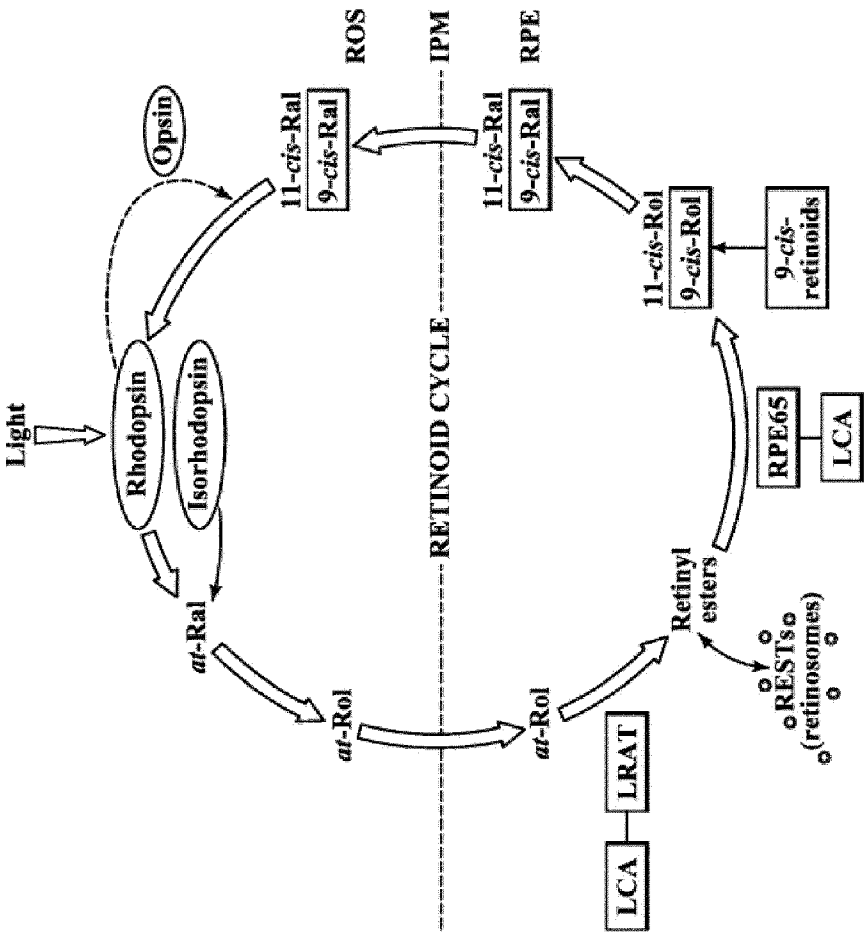

Figure 1

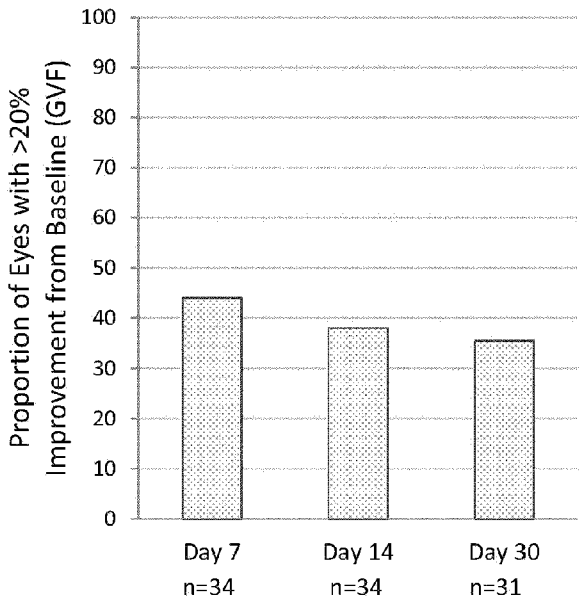

Figure 2A

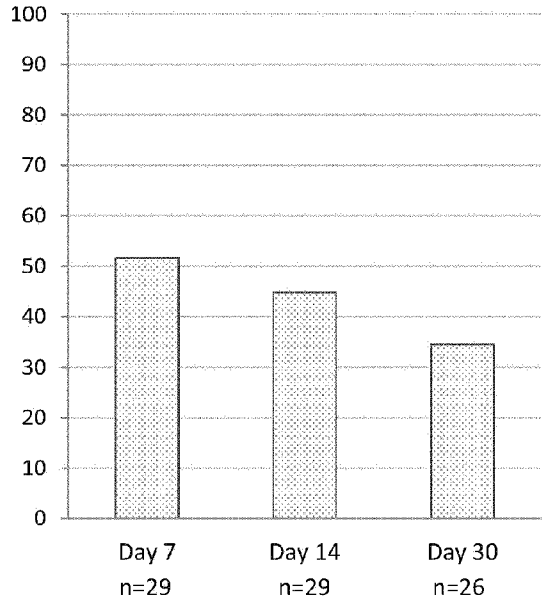

Figure 2B

Figure 3A

Figure 3B

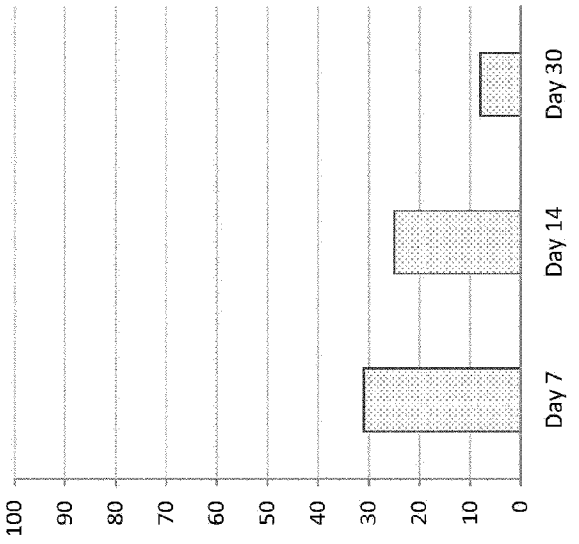

Figure 4B

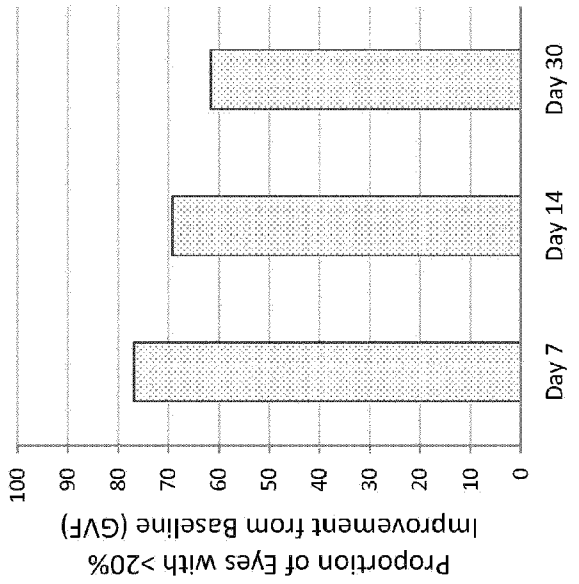

Figure 4A

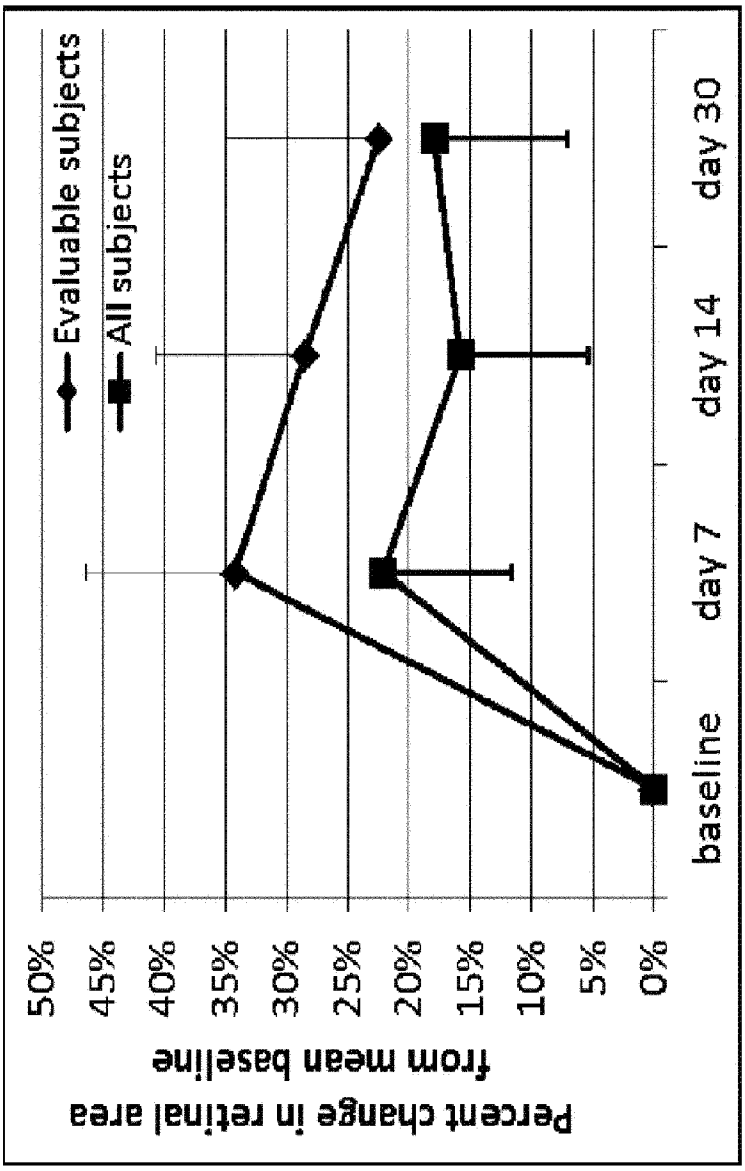
Percent change in retinal area from mean baseline
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
baseline
day 7
day 14
day 30
Evaluable subjects
All subjects

Figure 5

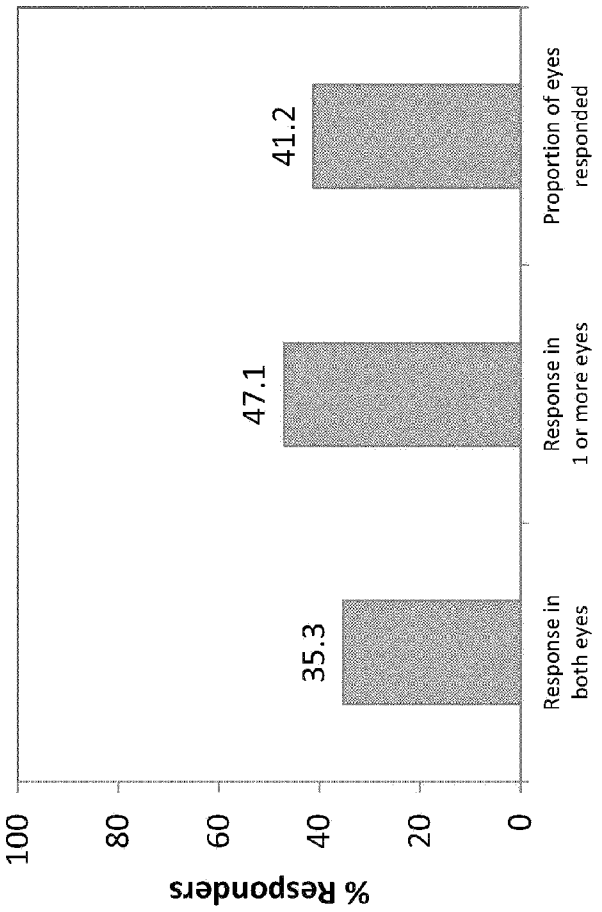
% Responders
100
80
60
40
20
0
35.3
47.1
41.2
Response in both eyes
Response in 1 or more eyes
Proportion of eyes responded

Figure 6

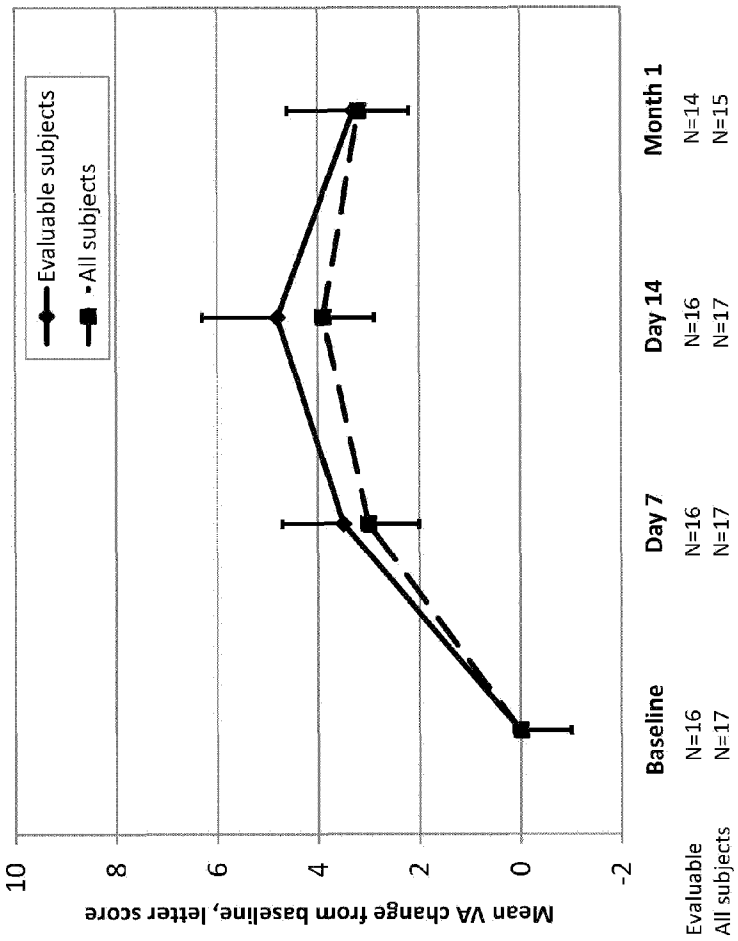
Evaluable subjects
All subjects
Mean VA change from baseline, letter score
10
8
6
4
2
0
-2
Baseline
Day 7
Day 14
Month 1
Evaluable
N=16
N=16
N=16
N=14
All subjects
N=17
N=17
N=17
N=15

Figure 7

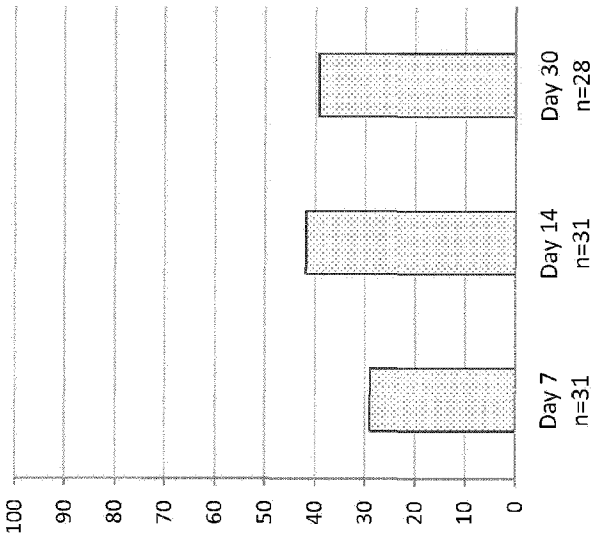

Figure 8B

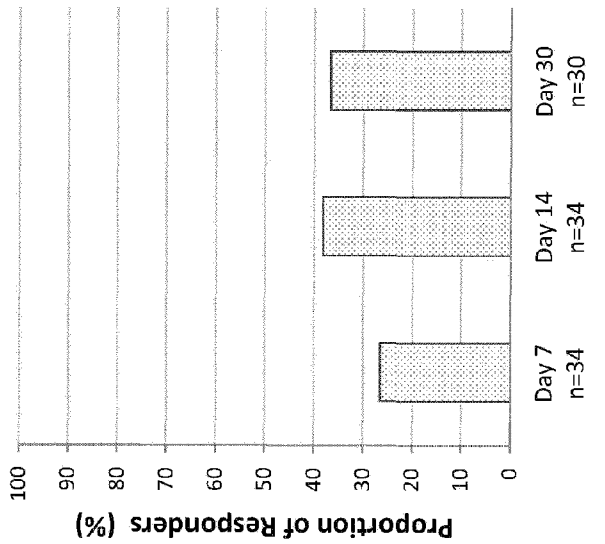

Figure 8A

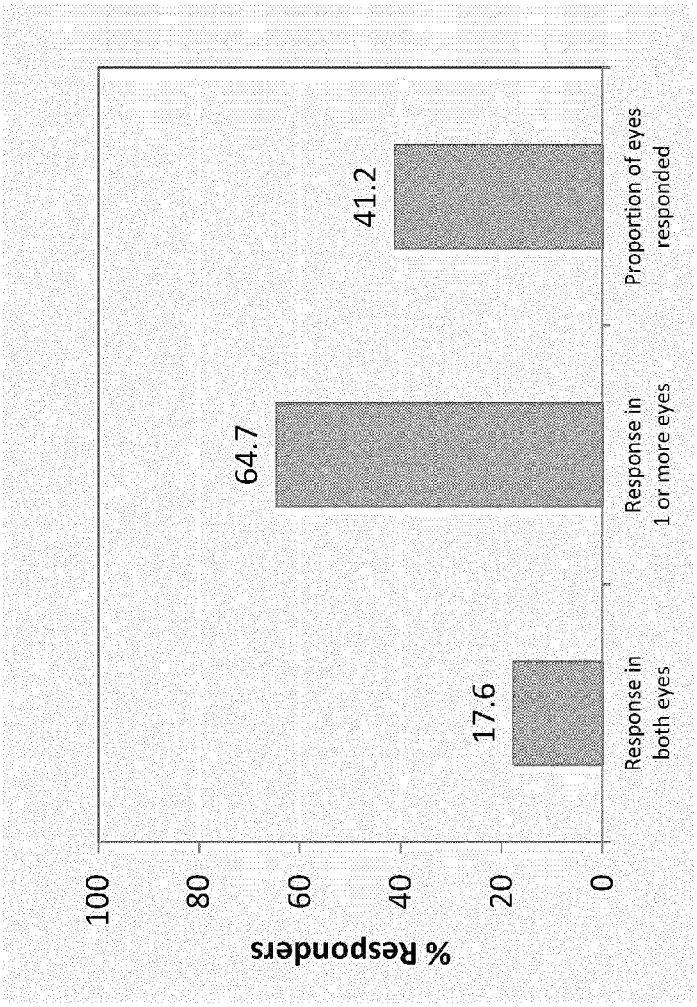
% Responders
100
80
60
40
20
0
17.6
64.7
41.2
Response in both eyes
Response in 1 or more eyes
Proportion of eyes responded

Figure 9

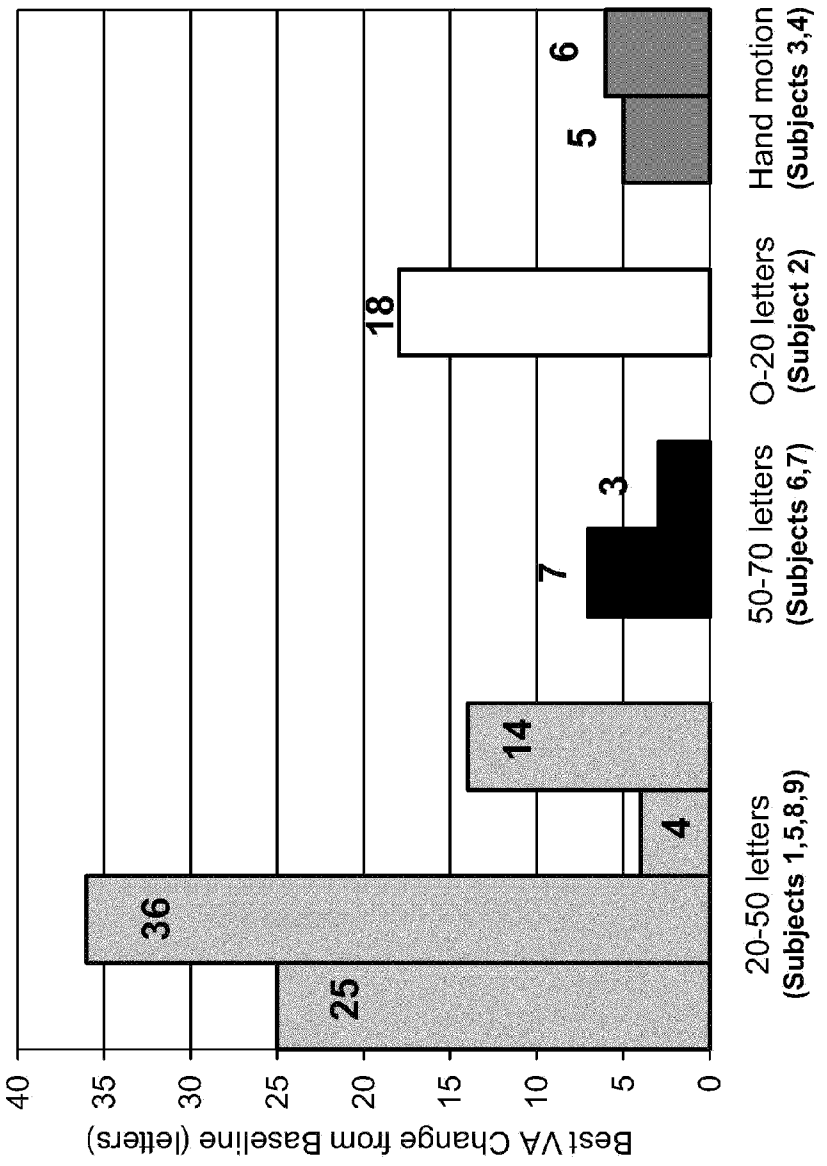
Best VA Change from Baseline (letters)
40
35
30
25
20
15
10
5
0
36
25
14
4
7
3
18
5
6
20-50 letters (Subjects 1,5,8,9)
50-70 letters (Subjects 6,7)
O-20 letters (Subject 2)
Hand motion (Subjects 3,4)
Baseline VA Category

Figure 10

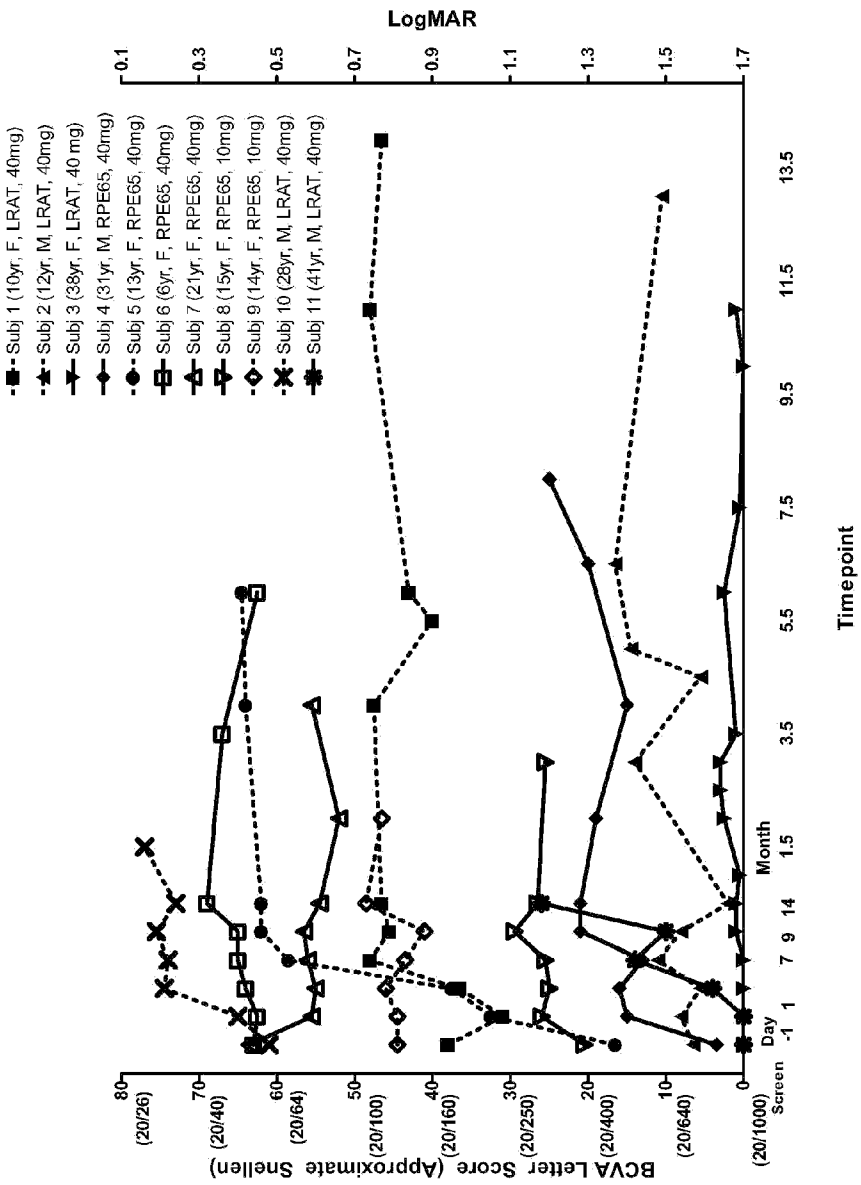
LogMAR
0.1
0.3
0.5
0.7
0.9
1.1
1.3
1.5
1.7
Subj 1 (10yr, F, LRAT, 40mg)
Subj 2 (12yr, M, LRAT, 40mg)
Subj 3 (38yr, F, LRAT, 40 mg)
Subj 4 (31yr, M, RPE65, 40mg)
Subj 5 (13yr, F, RPE65, 40mg)
Subj 6 (6yr, F, RPE65, 40mg)
Subj 7 (21yr, F, RPE65, 40mg)
Subj 8 (15yr, F, RPE65, 10mg)
Subj 9 (14yr, F, RPE65, 10mg)
Subj 10 (28yr, M, LRAT, 40mg)
Subj 11 (41yr, M, LRAT, 40mg)
BCVA Letter Score (Approximate Snellen)
80 (20/26)
70 (20/40)
60 (20/64)
50 (20/100)
40 (20/160)
30 (20/250)
20 (20/400)
10 (20/640)
0 (20/1000)
Screen
Day -1 1 7 9 14
Month 1.5 3.5 5.5 7.5 9.5 11.5 13.5
Timepoint

Figure 11

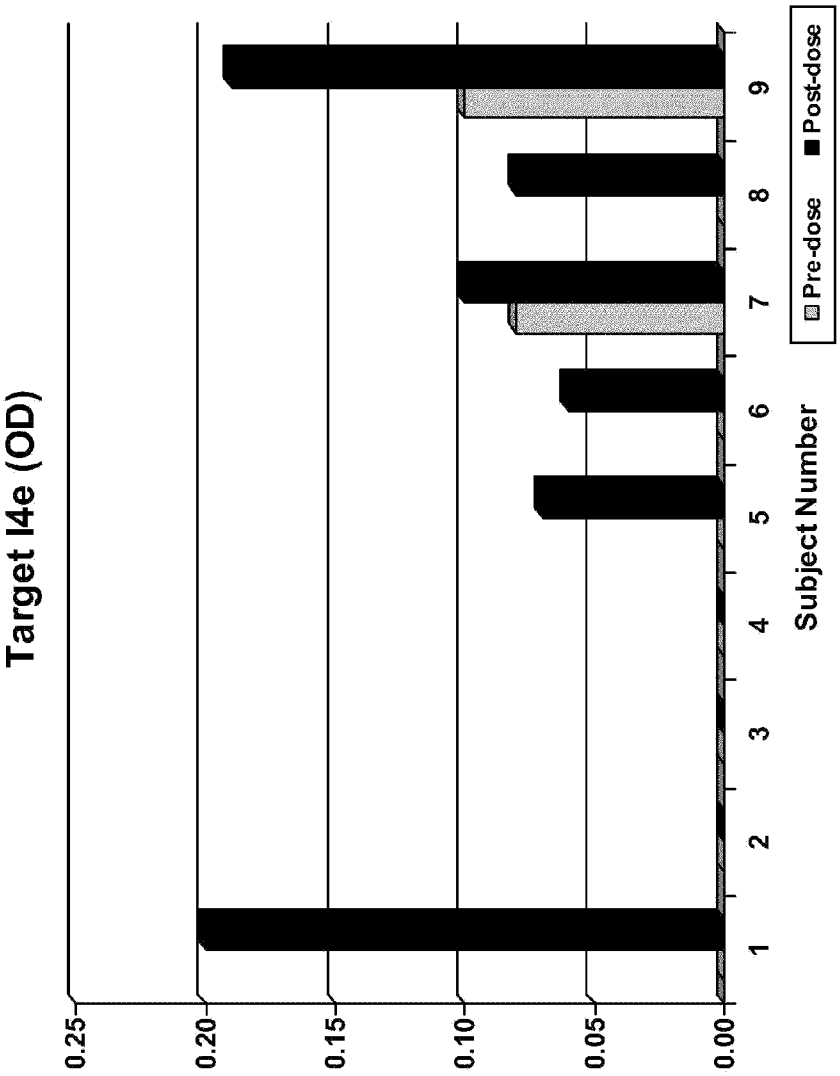
Target I4e (OD)
0.25
0.20
0.15
0.10
0.05
0.00
1
2
3
4
5
6
7
8
9
Subject Number
Pre-dose
Post-dose

Figure 12

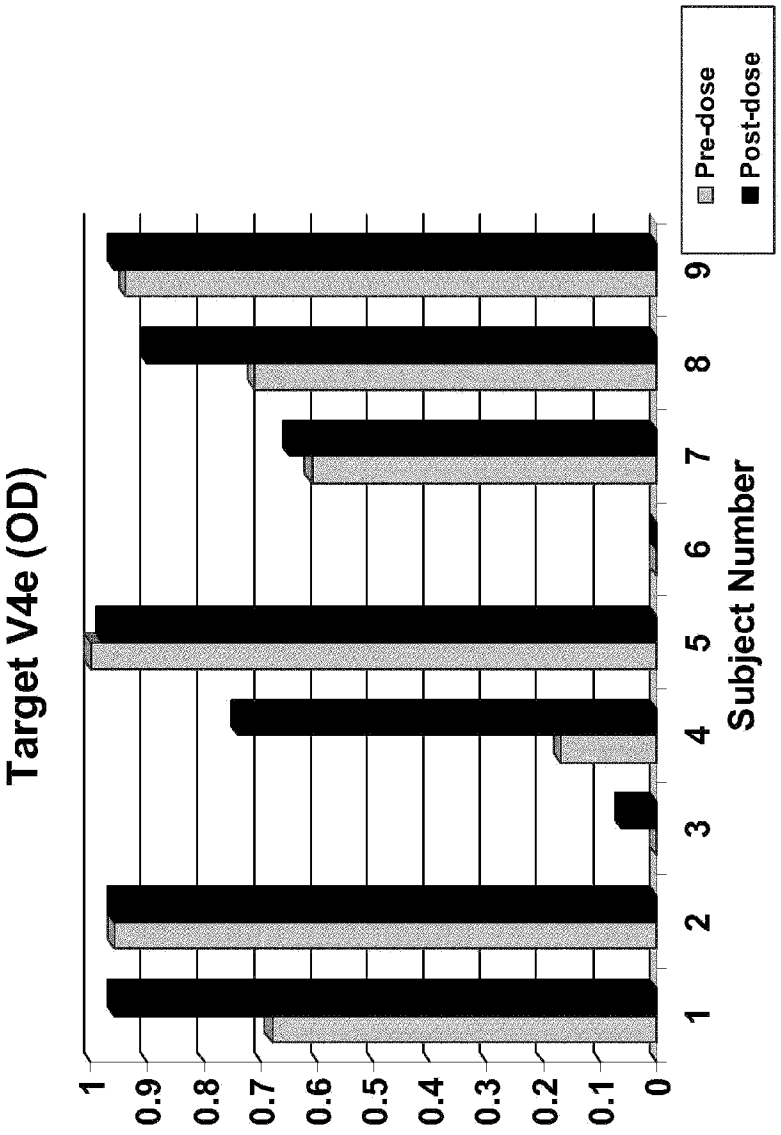
Target V4e (OD)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
7
8
9
Subject Number
Pre-dose
Post-dose

Figure 13

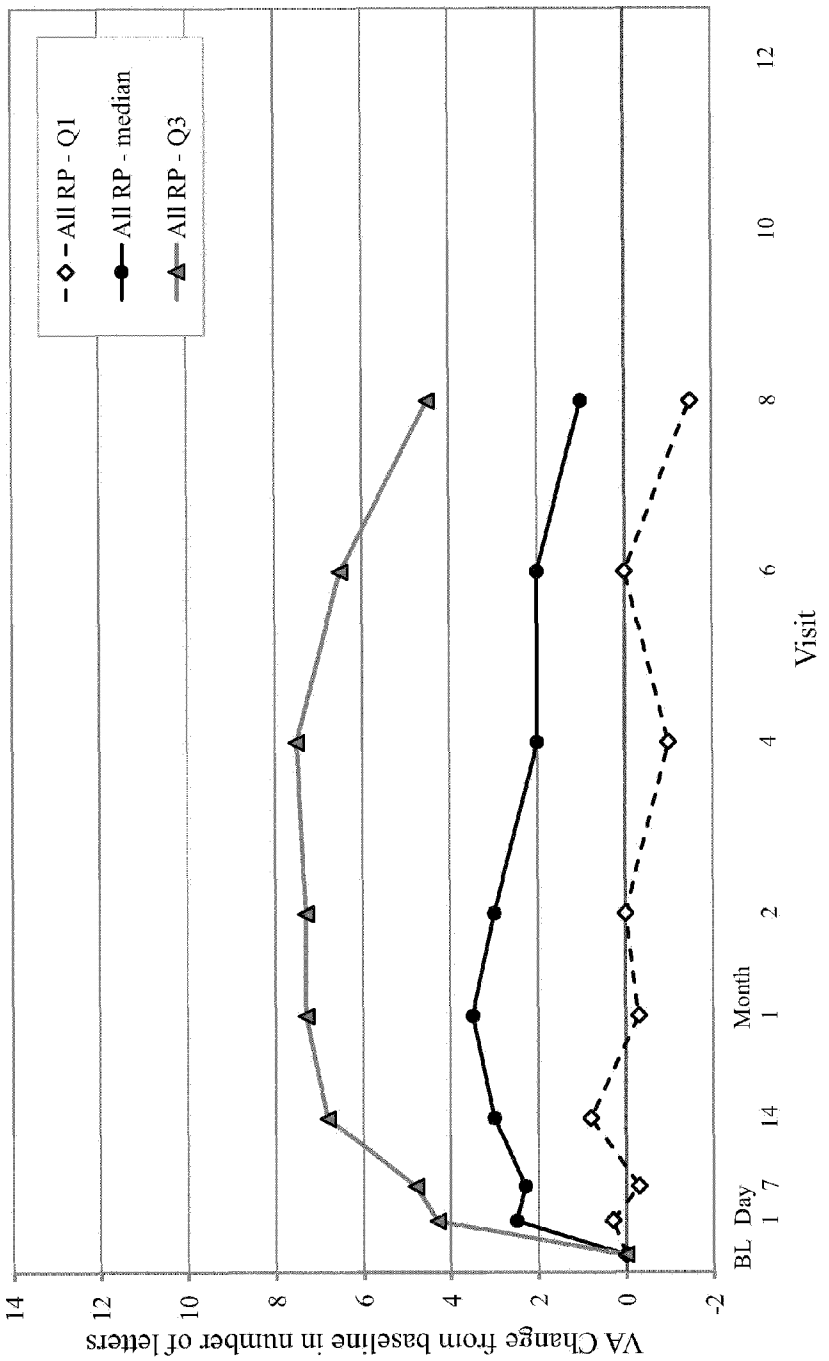
All RP - Q1
All RP - median
All RP - Q3
VA Change from baseline in number of letters
14
12
10
8
6
4
2
0
-2
BL
Day
1
7
14
Month
1
2
4
6
8
10
12
Visit

Figure 14