Revakinagene taroretcel-lwey (ENCELTO)
National Drug Monograph
June 2025

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Revakinagene taroretcel-lwey is an allogeneic encapsulated cell-based gene therapy

Indication(s) Under Review in This Document

Revakinagene taroretcel-lwey is indicated for the treatment adults with idiopathic macular telangiectasia type 2 (MacTel)

Dosage Form(s) Under Review

- A single-dose implant containing 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotropic factor (rhCNTF) for intravitreal surgical placement

Clinical Evidence Summary[1,4]

Efficacy Considerations

- The efficacy of revakinagene, supporting its FDA approval, was evaluated from industry-sponsored studies, including two studies, Study NTMT-03-A (NCT03316300; Study 1) and Study NTMT-03-B (NCT03319849; Study 2). Both Study 1 and Study 2 were randomized, multicenter, sham-controlled studies which enrolled adults with idiopathic macular telangiectasia type 2 (MacTel)
- Patients were required to have a photoreceptor inner segment/outer segment (IS/OS PR) break (loss) in ellipsoid zone (EZ) between 0.16 and 2.00 mm2 measured by spectral domain-optical coherence tomography (SD-OCT) and best corrected visual acuity (BCVA) of 54-letter score or better (20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart
- Patients with neovascular MacTel were excluded. (Table 1)
- Patients were randomized to receive either revakinagene intravitreal implant or sham procedure under standard operative procedures

- Patients in the revakinagene group underwent conjunctival peritomy, implant placement in the vitreous cavity via sclerotomy and closure with sutures. Patients in the Sham group underwent conjunctival peritomy, scleral pressure, and conjunctival closure with sutures.
- A total of 120 patients (Study 1) were randomized and of these, 115 patients (revakinagene group: 58; sham group: 57) comprised the efficacy analysis population while 119 patients were randomized in Study 2 and of these, 113 patients (revakinagene group: 59; sham group: 54) comprised the efficacy analysis population
- The primary efficacy outcome measure was the rate of change in the area of EZ loss (IS/OS, macular PR loss) over 24 months, as measured by SD-OCT. The area of EZ loss (EZ break) was measured in enface OCT at different time points from baseline to month 24 and the rate of change from baseline to month 24 was calculated. Slowing of the rate of EZ loss reflects photoreceptor preservation and clinical benefit through preserving retinal health and visual function
- The secondary outcome measure was the mean change in aggregate sensitivity loss of microperimetry within the EZ break area from baseline to month 24. Microperimetry is a procedure to assess retinal sensitivity while fundus is directly examined; it enables exact correlation between macular pathology and corresponding functional abnormality
- Study participants largely included white middle-aged women which may not reflect the VA population (Table 2)
- Study 1 and Study 2 showed a significant difference in the rate of change in EZ area loss from baseline over 24 months (primary outcome) between revakinagene and sham treatment (Table 3)
- The difference in mean change in aggregate retinal sensitivity loss of microperimetry from baseline to 24 months (secondary outcome) was significant in Study 1 but not in Study 2 (Table 4).
- Adverse reactions were common (Table 5)

Table 1. Key Inclusion and Exclusion Criteria for NTMT-03-A and NTMT-03-B[1]

Inclusion
• Participant must have at least one study eye with a positive diagnosis of MacTel with evidence of fluorescein leakage typical of MacTel and at least one of the other features that include hyperpigmentation that is outside of a 500-micron radius from the center of the fovea, retinal opacification, crystalline deposits, right-angle vessels, or inner/outer lamellar cavities • Participant must have an Inner Segment - Outer Segment Junction Line (IS/OS) Photo Receptor (PR) break in the study eye(s) and en face EZ (area of IS/OS loss) as measured by spectral-domain optical coherence tomography (SD-OCT) between 0.16 mm^2 and 2.00 mm^2 • Participant's best corrected visual acuity (BCVA) is a 54-letter score or better (20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at screening. • Participant must have steady fixation in the foveal or parafoveal area and sufficiently clear media for good quality photographs • Participant must be greater than 21 years of age or less than 80 years of age at screening

- Participant must be able to provide written informed consent to participate in the study, in accordance with the International Conference on Harmonisation Good Clinical Practices guidelines, and local regulations, before initiating any study-related procedures
- Women of childbearing potential must agree to use highly effective contraception (Germany and France only)

Exclusion

- Participant is medically unable to comply with study procedures or follow-up visits
- Participant received intravitreal steroid therapy for non-neovascular MacTel within the last 3 months
- Participant has ever received intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye OR has, within the past 3 months, received intravitreal anti-VEGF in the fellow eye at randomization
- Participant has evidence of ocular disease other than MacTel that, in the judgment of the examining physician, may confound the diagnosis, procedures or outcome of the study (eg, glaucoma, severe nonproliferative or proliferative diabetic retinopathy, uveitis)
- Participant has a chronic requirement (e.g., ≥ 4 weeks at a time) for ocular medications and/or has a diagnosed disease that, in the judgment of the examining physician, may be vision threatening or may affect the primary outcome (artificial tears are permitted)
- Participant has evidence of intraretinal **neovascularization** or subretinal neovascularization (SRNV), as evidenced by hemorrhage, hard exudate, subretinal fluid or intraretinal fluid in either eye
- Participant has evidence of central serous chorio-retinopathy in either eye
- Participant has evidence of pathologic myopia in either eye
- Participant has significant corneal or media opacities in either eye
- Participant has had a vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
- Participant has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the Age-Related Eye Disease Study (AREDS) clinical lens grading system
- Participant has undergone lens removal in the previous 3 months or YAG laser within 4 weeks
- Participant was a participant in any other clinical trial of an intervention (drug or device) within the last 6 months
- Participant is on chemotherapy
- Participant is pregnant or breastfeeding
- Participant has a history of malignancy that would compromise the 24-month study survival
- Participant with a history of ocular herpes virus in either eye
- Participant has, in the opinion of the investigator, any physical or mental condition that would increase the risk of participation in the study or may interfere with the study procedures, evaluations, and outcome assessments
- Participant has evidence of intraretinal hyperreflectivity by optical coherence tomography (OCT)

Table 2. Baseline Characteristics of NTMT-03-A and NTMT-03-B Participants [1,4]

Characteristic	NTMT-03-A N=115	NTMT-03-B N=113
Age, years, mean (range)	61 (40-78)	59 (40-75)
% Female	69	73
Race/ethnicity, n (%)		
White	98 (85)	102 (90)
Black	3 (3)	0
Asian	5 (4)	4 (4)
American Indian	1 (1)	0
Other	8 (7)	7 (6)
Hispanic	6 (5)	8 (7)
EZ area, median (min, max), mm^2		
Revakinagene	0.35 (0.15, 1.99)	0.48 (0.16, 1.63)
Sham	0.36 (0.16, 1.7)	0.39 (0.16, 1.38)
Aggregate sensitivity of microperimetry within the EZ break area, median (min, max) dB		
Revakinagene	35.2 (0.75, 398.8)	40.07 (4.82, 291.52)
Sham	35.5 (2, 281.3)	28.86 (0.33, 221.17)

EZ: ellipsoid zone

Table 3. Primary Endpoint, Study NTMT-03-A (NCT03316300; Study 1) and Study NTMT-03-B (NCT03319849; Study 2) [1,4]

Study 1	Revakinagene (RT) N=58	Sham N=57	Difference RT-Sham	P-value
Rate of change in EZ area loss from baseline over 24 months mm^2 (95% CI)	0.075 (0.05, 0.10)	0.166 (0.14, 0.19)	-0.091 (-0.13, -0.06)	<0.0001
Study 2	**N=59**	**N=54**		
Rate of change in EZ area loss from baseline over 24 months mm^2 (95% CI)	0.111 (0.08, 0.14)	0.160 (0.13, 0.19)	-0.049 (-0.089, -0.008)	0.0186

CI: confidence interval; EZ: ellipsoid zone

Table 4. Secondary Endpoints, Study NTMT-03-A (NCT03316300; Study 1) and Study NTMT-03-B (NCT03319849; Study 2) [1,4]

Study 1	**Revakinagene (RT) N=58**	**Sham N=57**	**Difference RT-Sham**	**P-value**
Mean change in aggregate retinal sensitivity loss from baseline to 24-months dB (95% CI)	25.27 (15.88, 34.67)	43.02 (31.78, 54.26)	-17.75 (-32.58, -2.91)	0.02
Study 2	**N=59**	**N=54**		
Mean change in aggregate retinal sensitivity loss from baseline to 24-months dB (95% CI)	40.02 (26.08, 53.96)	41.97 (30.34, 53.60)	-1.95 (-20.33, 16.43)	0.83

CI: confidence interval

Safety Considerations

Contraindications:

- Active or suspected ocular or periocular infections
- Known hypersensitivity to Endothelial Serum Free Media (Endo-SFM)

Warnings / precautions [1]

- Severe vision loss
- Infectious endophthalmitis
- Retinal tear and detachment
- Vitreous hemorrhage
- Implant extrusion
- Cataract formation
- Suture related complications
- Delayed dark adaption

Table 5. Common adverse reactions occurring in patients who participated in Study 1 and Study 2[1,4]

	Revakinagene N=117 N (%)	Sham N=111 N (%)
Conjunctival hemorrhage	36 (31)	29 (26)
Delayed dark adaptation	27 (23.1)	1 (1)
Foreign body sensation in eyes	18 (15)	15 (13.5)
Eye pain	18 (15)	10 (9)
Suture related complication	18 (15)	3 (2.7)
Miosis	18 (15)	0 (0)
Conjunctival hyperemia	13 (11)	9 (8)
Eye pruritus	10 (9)	4 (3.6)
Ocular discomfort	10 (9)	1 (1)
Vitreous hemorrhage	10 (9)	0 (0)
Vision blurred	8 (7)	4 (4)
Headache	8 (7)	1 (1)
Dry eye	7 (6)	2 (2)

Other Therapeutic Options

Table 6.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Revakinagene	NF	Idiopathic macular telangiectasia type 2 (MacTel)	For **Non** Neovascular MacTel
Aflibercept	F	Diabetic retinopathy, Macular degeneration, Macular edema, Retinopathy of prematurity	Off label for Neovascular MacTel
Bevacizumab	NF	Cervical, colorectal, hepatocellular, non-small cell, ovarian, and renal cell carcinoma. Glioblastoma	Off label for Macular degeneration
Faricimab	F	Macular degeneration, Macular edema	Off label for Neovascular MacTel
Ranibizumab	F	Diabetic retinopathy, Macular degeneration, Macular edema, Myopic choroidal neovascularization	Off label for Neovascular MacTel

Projected Place in Therapy

- Macular telangiectasia (MacTel) is a rare retinal disease affecting the macula, causing loss of central vision. Central vision is what you see in the center of your visual field and is used for tasks such as driving, reading, and recognizing faces.
- The results of Study 1 and Study 2 support a beneficial effect of revakinagene in slowing EZ area loss compared to the sham surgery patients. Secondary outcomes were consistent with the primary efficacy results.
- Current formulary agents for the management of MacTel include the off-label use of anti-vascular endothelial growth factor (anti-VEGF) agents. Anti-VEGF agents appear to be most useful for neovascular MacTel. Revakinagene is approved for MacTel and is useful in managing non-neovascular MacTel.
- The most common adverse reactions associated with revakinagene are conjunctival hemorrhage, delayed dark adaption, foreign body sensation in eye, eye pain, suture related complications, and miosis.
- Revakinagene, in addition to anti-VEGF agents, provide options for the management of idiopathic macular telangiectasia type 2.

References

1. ENCELTO (revakinagene taroretcel-lwey) [prescribing information]. Neurotech Pharmaceuticals, Inc. Cumberland, RI. March 2025.
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4. Summary Basis for Regulatory Action. CBER Review Committee. March 5, 2025.
5. FDA BLA Approval #125798/0. U.S. Food and Drug Administration, Silver Spring, MD. March 5, 2025.
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Prepared June 2025. Contact person: Matthew A. Fuller, Pharm.D, BCPP, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)