Nanoscope Therapeutics' Comments on ICER Draft Background and Scope Document for Investigational *sonpiretigene isteparvovec*

Nanoscope Therapeutics (Nanoscope) provides the following comments on the draft Background and Scope document issued by ICER on September 17, 2024 for its evaluation of the clinical and economic outcomes of gene therapy with investigational *sonpiretigene isteparvovec* for the treatment of retinitis pigmentosa (RP). Nanoscope's comments focus on the components of Background, Outcomes, and Analyses (especially those related to Benefits Beyond Health and Special Ethical Priorities).

I. Comments on Background

Nanoscope recognizes the direct healthcare costs cited by ICER for the RP population. However, it is important to acknowledge that the direct costs cited are select costs that can be compared to similar interactions by healthy individuals with the healthcare system (Dr. visits, drugs prescribed, etc). For many RP patients, there are a variety of additional intersections with the healthcare system that are less comparable to anything a healthy individual that appears out of the scope of the cited study, but very much in the scope of the care path of RP patients. This can include significant training on the use of low-vision aids (canes, guide dogs, low-vision goggles), as well as functional therapy programs that help these individuals learn how to navigate familiar environments and remain safe within them. A significant time commitment is needed for this training to be effective and often requires a highly trained therapist in a one-on-one setting. It is therefore important to consider these factors in addition to the rate of Dr. visits and pharmaceuticals prescribed as compared to healthy individuals.

Furthermore, it is important to keep in mind the significantly higher societal cost incurred to accommodate severe vision loss patients. These patients undergo a complete loss of independence and full dependency on family members and caregivers. Additionally, those affected by RP lose the ability to perform any self-supporting vocation during a multi-decade period that comprises the most productive years in the workforce for individuals with normal vision. This a major societal burden since at least 2 otherwise fully productive individuals (the RP patient, and the caregiver) are removed from the workforce for every RP patient. In addition to this societal impact, there is a substantial cost that society bears to accommodate RP patients in the education system (special teachers, classrooms, teaching aids), public transport (specialized equipment on buses, trains, subways), and other recreational activities that is substantial.

Additionally, although RP is not fatal unto itself, the disruptive nature of the disease on quality of life is known to result in higher mortality among those affected. The impact that a loss of visual acuity on instrumental activities of daily living (VA $\geq$ 1.0 LogMAR) has been shown to be inclusive of a corresponding increase in mortality[1]. The substantial cost related to blindness-related depression and trauma in such severely impaired patients should be noted and accounted for.

Regarding the inclination to include *botaretigene sparoparvovec* as an intervention in our revised scope: It is important to note that *botaretigene sparoparvovec* is a different gene therapy

modality than *sonpiretigene isteparvovec*, each of which have different modality defined properties that make them hard to compare. In particular, *botaretigene sparoparvovec* is a classical gene therapy that is not applicable to severe vision loss patients that have already lost their photoreceptors. For this reason, classical gene replacement therapies like luxturna and *botaretigene sparoparvovec* intend to treat patients with better than 20/200 vision, that still have a significant proportion of photoreceptors. In contrast, *sonpiretigene isteparvovec* is intended to treat patients whose vision is 10X worse (e.g. 20/2000) in a gene agnostic manner in those that have already lost most, if not all photoreceptors. For this reason, it may not be useful to group *sonpiretigene isteparvovec* with classical gene therapies like those mentioned above.

II. Comments on Stakeholder Input

The self-description provided of an RP patient who equates their remaining vision to "looking through a pipe" with "no side vision" actually fits a less severe stage of the disease progression than that Nanoscope seeks to address with *sonpiretigene isteparvovec.* Target patients for *sonpiretigene isteparvovec* have few or no remaining photoreceptors and no functional vision remaining. They do not have either peripheral or central vision. They may not even detect when a light is ON or which direction the light is coming from.

III. Comments on Outcomes

It is very well known through the natural history of this advanced RP patient population that visual acuity loss is the most detrimental outcome. For this reason, visual acuity should be considered the most critical Patient-Important-Outcome parameter to gauge the treatment benefit.

Regarding outcomes related to independence in daily life, many of the severe RP patients report that driving (which can be obtained by ride-share app etc) is not as meaningful of an outcome to them as other basic activities of independence. These patients have lost nearly all of their vision, and they can no longer independently perform many activities that utilize vision below the requirement to drive. For this reason, a focus on the following activities is recommended instead of driving: Picking up objects from a shelf (e.g. medicine from a medicine cabinet, finding a door knob, soap in the bathroom, or food from a refrigerator), knowing the presence of other individuals in the room/elevator (avoiding collision with other people), attending to personal hygiene (being able to navigate to the bathroom and brush teeth, take shower etc).
In the case of mobility, it is particularly meaningful to these patients to be able to find a lighted window or doorway and navigate to it, identify exit doors, and even the position of a table with a table lamp in a room.

IV. Comments on Scope of Comparative Value Analyses

The indirect costs due to severe vision impairment may be calculated as a linear function of visual acuity. This is based on national surveys of patients with RP on productivity loss, caregiver burden, and government program loss[2,3]. Health-related quality of life (HRQoL) can be based on a linear function of VA: Based on a study that elicited standard gamble (SG) utility from patients with diabetes, patients with diabetic retinopathy, and general public [4].

Previously used linear function, supported by data, allows for more granular relationship between VA and health utilities. This is the same as that of the ICER CEM of Luxturna®, which has been published and peer-reviewed[5,6].

Additionally, it may be noted that total healthcare costs (direct and indirect healthcare costs) do not include societal costs, caregiver productivity loss, and government program costs. As a result, it is fundamental to a comprehensive analysis to include health-related QoL assessments, incremental cost-effectiveness ratios, life expectancy, and quality-adjusted life expectancy are fundamental in health economic modeling.

V. Comments on Identification of Low-Value Services

While low-value services such as the provision of audio-guided navigation systems are of value to low-vision RP patients, it should be noted that the inability to see objects and perceive light has a much greater psychological impact inclusive of disruption of the sleep-wake cycle of these patients. This disruption persists despite the effective use of low-vision aides (especially such as audio-guided navigation) since it depends on the light sensation and actual vision of an individual. For these reasons, vision improvements in these patients promote the return of a healthier sleep-wake cycle alongside the other independence-related improvements in quality of life, and should be valued accordingly in any analysis.

References

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