Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000126: Functional Vision Questionnaire (FVQ) PRO
Letter of Intent

Administrative Structure:

This proposal is being submitted by Novartis Pharmaceuticals Corporation which is the sponsor of the PRO. Novartis has contracted with Adelphi Values, a health outcomes agency commissioned to conduct research supporting the development of the PRO. Please direct correspondence to Orin Tempkin.

Primary contact: Dr. Orin Tempkin
Executive Director, Regulatory Affairs
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
(862) 778-6949
orin.tempkin@novartis.com

Dr. Judit Banhazi
Global HEOR Associate Director
New Products
Novartis Pharma AG
Basel, Switzerland
+41 61 324 2090
judit.banhazi@novartis.com

Dr. Francesco Patalano
Head of Center of Excellence - Patient-Reported Outcomes
Novartis Pharma AG
Basel, Switzerland
+ 41 61 324 8040
francesco.patalano@novartis.com.

Rob Arbuckle
Managing Director
Adelphi Values
Patient-Centered Outcomes
Bollington, Cheshire, UK
SK10 5JB
+44 (0) 1625 578865
rob.arbuckle@adelphivalues.com

Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

The concepts of interest are visual function and functional vision in adolescent (12-17 years) and adult (18 years or older) patients with a clinical and genetic confirmed diagnosis of Retinitis Pigmentosa (RP). Currently in qualitative development, the Functional Vision Questionnaire (FVQ) Patient-Reported Outcome (PRO) includes domains targeted to assess those concepts in adolescent (12- 17 years) and adult (18 years or older) patients. The current version of the FVQ (version 2.0) includes 13 items in the visual function domain, 22 items in the functional vision domain and 13 items in the distal health-related quality of life (HRQoL) domain.

It should be noted that an associated FVQ Observer-Reported Outcome (ObsRO) is also being developed for use with caregivers of children aged 3 to 11 years and is being submitted simultaneously as part of a parallel COA Qualification Letter of Intent.

Conceptual framework

Table 2-1 below provides the conceptual framework for the functional vision and visual functioning domains of the current version of the FVQ PRO instrument (version 2.0). The draft FVQ PRO is designed to assess functional vision and visual functioning by measuring the level of difficulty or frequency experienced by RP patients when in specific situations or performing a variety of activities of daily living (ADLs) that significantly rely on visual function.

The draft 48-item FVQ PRO currently consists of three domains assessing visual function symptoms (13 items; night blindness, light/dark adaptation, vision in bright lighting, contrast sensitivity, difficulty seeing color, loss of peripheral vision, distance vision and depth perception), impacts on functional vision (22 items; including daily activities and mobility). There are also 13 items assessing impacts on distal HRQoL (13 items; social functioning; interpersonal and family relationships, emotional wellbeing, work and education and leisure activities). To date, the first round of combined concept elicitation and cognitive debriefing interviews has been completed. The conceptual framework will be refined and updated if the PRO is modified after the completion of the qualitative interviews.

Table 2-1 Conceptual framework for the domains of the FVQ PRO (version 2.0)

Domain	Sub-domain	Concept	Item
Visual function symptoms	Night blindness		1. Difficulty seeing outside with street lighting on a dark night
	Light/dark adaptation		2. Difficulty adjusting from darkness to good lighting
			3. Difficulty adjusting from good lighting to darkness
			4. Difficulty adjusting from good lighting to very bright lighting
	Vision in bright lighting		5. Difficulty seeing in very bright lighting once adjusted to the lighting
			6. Difficulty seeing in fluorescent lighting
	Contrast sensitivity		7. Difficulty seeing furniture in dimly lit rooms with dark floors
	Difficulty seeing color		8. Difficulty telling the difference between different colors in good light
	Loss of peripheral vision		9. Difficulty noticing objects off to the side when walking outdoors in daylight
			10. Difficulty noticing objects off to the side when walking outdoors in dim lighting
	Distance vision	Middle distance	11. Difficulty seeing things that are on the other side of the room
		Long distance	12. Difficulty seeing things that are far away
	Depth perception		13. Difficulty judging how far away things are from you
Impacts on functional vision	Daily activities	Reading normal print	14. Difficulty reading normal size print in a room with good lighting
			15. Difficulty reading normal size print in a dimly lit room
		Reading street signs	16. Difficulty reading street signs when walking outside in daylight
			17. Difficulty reading street signs when walking outside in dim light
		Finding things in familiar environment	18. Difficulty finding an object on a crowded shelf in a room in your own home with good lighting
			19. Difficulty finding an object in a dimly lit room at home in your own home
		Driving*	20. Difficulty driving in dim lighting
		Finding things in unfamiliar environments	21. Difficulty finding things when moved from their usual place in a room with good lighting
		Viewing digital screens	22. Difficulty seeing things on a computer screen
			23. Difficulty seeing things on a mobile phone or tablet
			24. Difficulty watching tv
		Household chores	25. Difficulty doing household chores
		Self-care	26. Difficulty with self-care activities
		Eating	27. Difficulty seeing food on your plate in a dimly lit room

Table 2-1 Conceptual framework for the domains of the FVQ PRO (version 2.0)

Domain	Sub-domain	Concept	Item
	Mobility	Navigating/mobility in unfamiliar environments	28. Difficulty walking in unfamiliar outdoor places by yourself without help in dim lighting
		Navigating/mobility in dark or dim light	29. Difficulty walking in familiar outdoor places by yourself without help in dim lighting
		Going up/down steps and stairs	30. Difficulty going down steps, stairs, or stepping off a curb in good lighting without help from someone else
			31. Difficulty going down steps, stairs, or stepping off a curb in dim lighting without help from someone else
		Bumping into objects/people	32. Bumping into objects or people when walking in unfamiliar places in dim lighting
			33. Bumping into objects when they were moved from their usual spot when walking in a room with good lighting
		Falling/tripping	34. Tripping or falling when walking in familiar outdoor places by yourself in daylight
			35. Tripping or falling when walking in familiar outdoor places by yourself in dim lighting
Impacts on distal HRQoL	Leisure activities		36. Difficulty doing outdoor leisure activities in daylight
			37. Difficulty doing outdoor leisure activities in dim lighting
			38. Difficulty doing indoor leisure activities in good lighting
			39. Difficulty doing indoor leisure activities in a dimly lit room
	Social functioning	Recognizing facial expressions	40. Difficulty seeing reactions on people's faces in a room with good lighting
		Recognizing faces	41. Difficulty recognizing people's faces in a room with good lighting
		Going to social events	42. Difficulty going to social events in dim lighting
	Interpersonal/ family relationships	Independence	43. Relying on others for help
	Emotional well-being	Frustration	44. Felt frustrated
		Embarrassment	45. Felt embarrassed
		Depression	46. Felt depressed
		Worry	47. Felt worried that you may fall or be injured
	Work and school		48. Difficulty at work or school

*Impacts on driving will only be relevant to a subset of RP patients. **Grey cells** - qualification is not being pursued for these items.

Context of Use for COA Qualification:

Targeted study population

The FVQ PRO instrument is intended to be used to assess visual function and functional vision in adolescent (12-17 years) and adult (18 years or older) patients with a clinical and genetic confirmed diagnosis of RP. The target population includes adolescent and adult patients with different RP gene mutations, including *RLBP1* and *RPE65*, with the exception of Usher Syndrome as this subtype is associated with both visual and aural impairments. Clinical trial samples are expected to include adolescent and adult RP patients with demographically and clinically diverse characteristics including diversity in terms of age, RP subtype, patient-reported severity, visual acuity and country. The FVQ PRO is intended to be used in RP clinical trials to evaluate the efficacy of RP treatments (most likely gene therapies) across multiple countries and languages.

RP refers to a group of inherited degenerations of the photoreceptor cells (rods and cones) of the retina leading to gradual loss of vision and ultimately blindness. Patients with RP typically lose night vision in adolescence, peripheral vision in young adulthood, and central vision in later life, all of which affect patients' ability to perform vision-dependent functions of everyday life [1]. Mutations in any of a wide variety of genes can cause RP.

It should be noted that findings from the qualitative phase will be used to explore if the relevant and important measurement concepts are the same (or different) for both adolescent and adult patients and whether a single instrument would be appropriate for both participant types. As noted above, an ObsRO is also being developed for use with caregivers of children aged 3-11 years which is being submitted in a separate, parallel Letter of Intent.

Targeted study design and statistical analysis plan

Following completion of the current qualitative phase of instrument development, an observational, non-interventional study will be conducted with adolescent and adult patients with RP to support initial assessment of the psychometric properties of the FVQ PRO for use with patients with different RP gene mutations. A psychometric analysis plan (PAP) will be developed and finalized prior to database lock detailing the psychometric analyses which will assess the performance of the FVQ PRO. Ability to detect change over time and anchor and distribution-based analyses to support estimation of within-patient and between-group meaningful change thresholds will then be evaluated in the first clinical trial(s) in which the instrument is included. The visual function and impact on functional vision scores resulting from the FVQ PRO instrument are expected to be used as secondary endpoints in RP clinical trials, with results used to provide evidence of treatment benefit and support product label claims. Other endpoints in RP trials are expected to include Performance-Reported Outcome (PerfO) assessments such as the Multi-Luminance Mobility Test (MLMT) and Clinician-Reported Outcome (ClinRO) assessments of concepts such as visual acuity or visual field.

Applicable study settings for future clinical trials

The FVQ PRO is being developed in English, German and French with qualitative research being conducted in the US, Canada (Newfoundland), France and Germany to help ensure the content is appropriate and applicable across cultures. It is intended for use in multinational clinical trials. Following completion of the qualitative development of the FVQ PRO it will be translated and linguistically validated for use in other non-English speaking languages. This process will follow best practice for linguistic validation, as detailed in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Translation and Cultural Adaptation Task Force best practice guidelines [2].

COA Type: Patient Reported Outcome (PRO)

References:

1. Hartong, D.T., E.L. Berson, and T.P. Dryja, *Retinitis pigmentosa.* The Lancet, 2006. **368**(9549): p. 1795-1809.

2. Wild, D., et al., *Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation.* Value Health, 2005. **8**(2): p. 94-104.