

EXPAND OCT substudy

OCT methodology

Sponsor: Novartis

EXPAND trial: NCT01665144

**A multicenter, randomized, double-blind, parallel-group,
placebo-controlled variable treatment duration study
evaluating the efficacy and safety of siponimod in patients
with secondary progressive multiple sclerosis**

Abbreviations

BPRC	Bern Photographic Reading Center
GCL	Ganglion cell layer
IPL	Inner plexiform layer
OCT	Optical coherence tomography
QC	Quality control
RNFL	Retinal nerve fiber layer
SD-OCT	Spectral domain-optical coherence tomography
SPMS	Secondary progressive multiple sclerosis

1. Project Summary

The Bern Photographic Reading Center (BPRC) is a research laboratory in the Bern University Hospital, Department of Ophthalmology, Inselspital, Bern, Switzerland, that provided independent assessment of optical images obtained in clinical trial NCT01665144, which is sponsored by Novartis Pharma AG and studied patients with secondary progressive multiple sclerosis (SPMS).

The imaging modalities employed in this study include Spectral Domain-Optical Coherence Tomography (SD-OCT). SD-OCT images were evaluated by the BPRC.

The BPRC provided clinical site training certification and support, image analysis and grading quality control, and maintained data integrity and security in a manner consistent with all applicable regulatory requirements.

2. Scope and Purpose

The purpose of this document is to describe how the evaluation of images were designed and conducted for the NCT01665144 clinical trial. The following are described within the document:

- Training of Imaging Specialists/Graders
- Site Certification
- Imaging Equipment
- Quality of Images
- Methodology of Review

3. Training of BPRC Imaging Specialists/Graders

Imaging specialists, or graders/readers, are the persons who read the images at the BPRC. Their backgrounds are within the medical profession, and range from medical technicians to medical doctors. Readers are regularly trained in reading OCT images. The BPRC has an internal training program with regular training sessions that occur at least 8 times per year.

The graders at the BPRC all received study-specific training. This training was conducted prior to the start of any study evaluations and included an introduction to the study protocol and all details on study-specific grading. All graders signed and dated a training log sheet. In addition, all graders are actively certified in Good Clinical Practice (GCP).

4. Site Certification

At each investigational site, at least one photographer must be certified to ensure an adequate and standardized quality and interpretation of the OCT images as defined in the study specific manuals. The investigational sites were strongly encouraged to have two certified photographers.

The certification of photographers was performed by the BPRC. The certification consisted of providing a set of OCT images for one patient (who did not necessarily have to qualify for the core study according to the inclusion/exclusion criteria listed in the NCT01665144 clinical study protocol). The image material had to be collected according to the study procedures and transmitted to BPRC, together with a ‘Certification Transmittal Log’, requesting certification. The Log had to contain information on the imaging system used by the site.

5. Imaging Equipment: Optical Coherence Tomography (OCT)

Spectralis™ HRA+OCT (Heidelberg Engineering, Germany)- standard ophthalmology software:

- Optic Nerve Head Scan

This scan acquired a circular scan line centered on the optic nerve head. It was used to measure the thickness of the retinal nerve fiber layer (RNFL).

- Volume Scan

This volume scan acquired the cube scans at 512 x 49 scans at 6.0mm x 6.0mm centered on the fovea. All scans had to be recorded in the “high speed” mode (HS).

Spectralis™ HRA+OCT (Heidelberg Engineering, Germany)- Nsite software:

- Optic Nerve Head Scans (ONHR-N)

This series of scans initially defined specific landmarks such as fovea and Bruch's Membrane Opening (BMO) in the retina to set the correct position of the Fovea-to-Disc-Axis (FoDI). All following scans were set according to the FoDi axis. The preset consisted of a star scan with 24 B-Scans followed by a series of 6 circular scans around the optic nerve head.

- Volume Scans (PPoleN)

A series of volume scans were acquired consisting of horizontally and vertically oriented B-scans aligned according to the defined FoDi (Fovea to Disc) axis, as defined in the ONHR-N preset.

Cirrus HD-OCT™ (Carl Zeiss Meditec, Germany)

- Optic Disc Cube Scan

This volume scan acquired the cube scans 200 x 200 scans

- Macular Cube Scan

This volume scan acquired the cube scans 200 x 200 scans and cube scans 512 x 128 scans

- Cross-Hair Scan (not used)

This scan consists of horizontal and vertical B-scans at the 6.0 mm scan length and 1024 A scans with the fixation on the macula and is automatically acquired during the macular cube scan.

6. Quality of Images

The procedures required for image acquisition at the ophthalmology sites are detailed in the study specific manuals. Images were required to be captured by a certified technician using certified equipment. In order to maintain objectivity in the evaluation of ophthalmic imaging, all images had to be submitted with the reading center blinded to participant name and date of birth.

Upon receipt, the images underwent a QC inspection by the image grader; this included verification of adherence to the study-specific imaging manuals:

- Information completeness (e.g., anonymization of data, subject identification (ID), image date)
- Image completeness: Presence of all required images per the visit schedule, correct image labelling and image quality

Images found to contain patient identifying information were to be removed from the system, and the site required to resubmit images to resolve the removal query.

The site was to be queried in case of missing imaging for a timepoint or incomplete imaging.

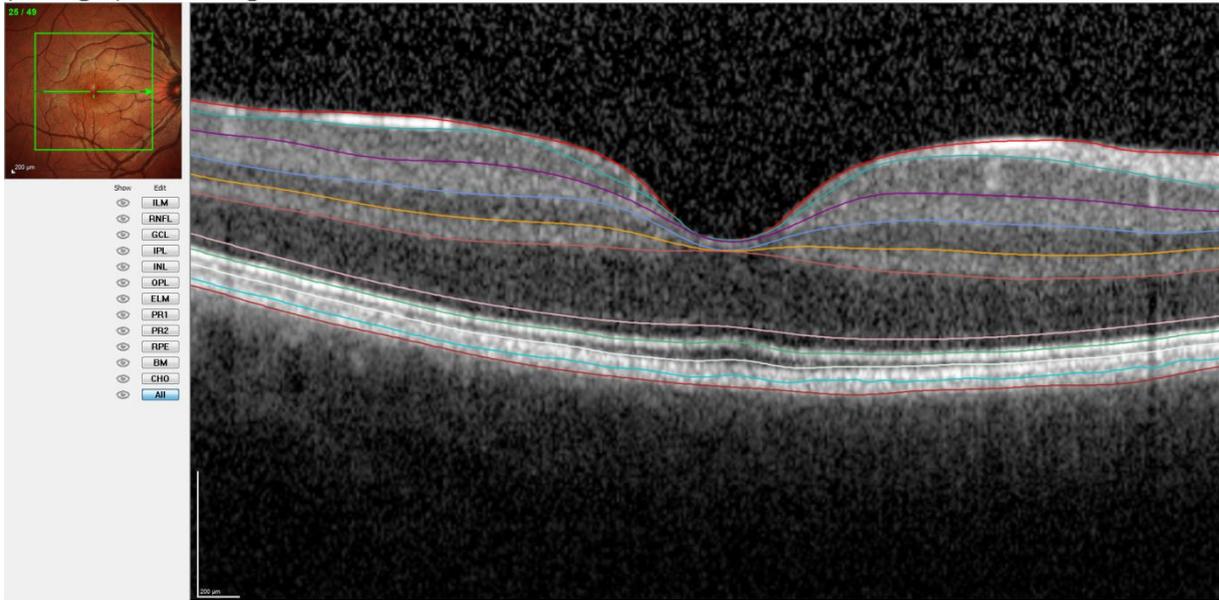
After query resolution, images underwent a second round of QC.

7. Methodology of Review

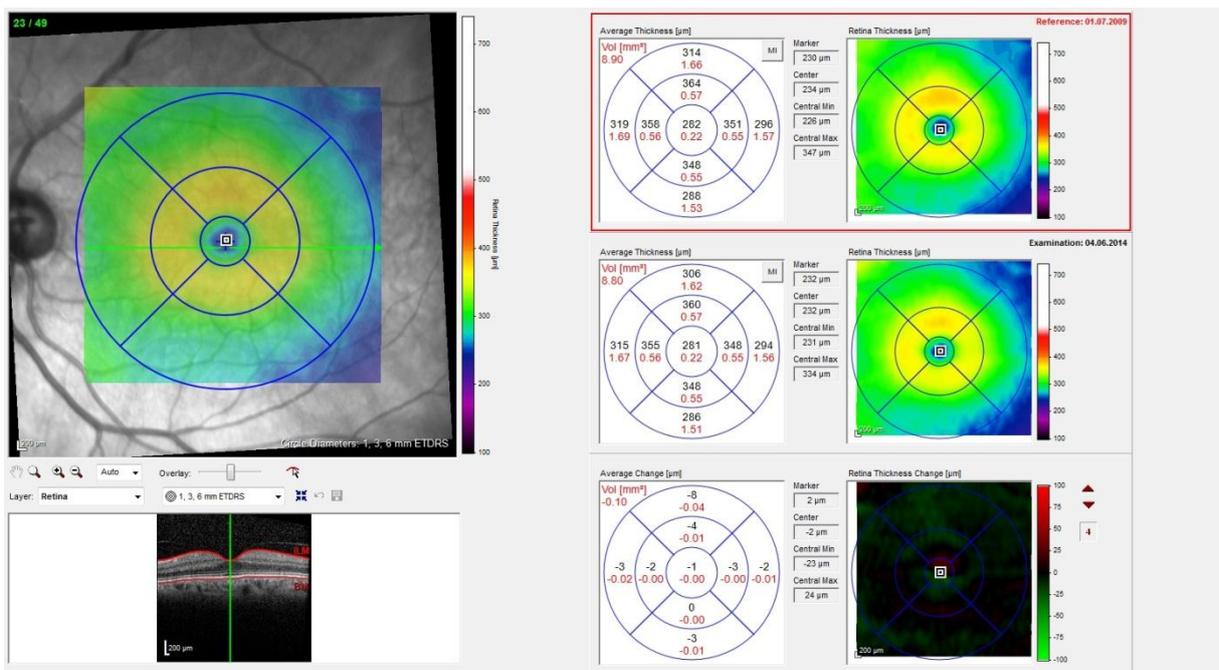
In this study, all images were graded using single step grading. While the single grader was not necessary the same person throughout the study, all graders are regularly trained in reading OCT images (see Section 3) and 10% of all gradings were randomly chosen and reviewed by a second grader for QC purposes. The grading task was carried out in the BPRC designated Webinterface.

OCT outcome measures, such as retinal thickness, ganglion cell layer (GCL) and inner plexiform layer (IPL) thickness, and RNFL thickness have been shown to correlate with clinical measures of vision loss and may facilitate visualization of any process of neurodegeneration, such as axonal loss, or repair as part of natural history of MS or as a consequence of neuroprotective interventions.

Retinal and GCL+IPL thickness was assessed from OCT volume scans (Spectralis) and macular cube scans (Cirrus). The measurement of the thickness of the different layers requires segmentation of the layers (see below).



For automatic segmentation the software provided by Heidelberg Engineering (for the Spectralis OCT) and by Zeiss (for the Cirrus OCT) is used. Each OCT scan is reviewed by a trained grader and segmentation errors are manually corrected. Thereafter, thickness maps are created. By overlaying the ETDRS grid, values for the central retina area and the 4 inner ring quadrants can be assessed.



Besides the measurements of the retinal layer thickness, the volume scans are assessed for morphologic alterations. These include microcystic macular edema, epiretinal membranes, vitreoretinal traction, and photoreceptor atrophy. Microcystic macular edema is diagnosed if small hyporefective areas in the inner nuclear layer (INL) are visible. Epiretinal membranes represent a hyperreflective band on the inner surface of the retina. Retinal traction is diagnosed if the inner surface of the retina is pulled towards the vitreous by a epiretinal membrane of the posterior vitreus. Photoreceptor atrophy is characterized by the lack of the photoreceptor layer in an OCT scan.

RNFL thickness is measured either from the optic nerve head scans (Spectralis OCT) or from the optic disc cube scan (Cirrus OCT). In these scans the RNFL is segmented in the same manner as the macular volume scans. All automatic resegmented scans are reviewed and segmentation is corrected manually if needed. The thickness is measured on a circular ring around the optic nerve head. Besides the main RNFL thickness on the ring (average RNFL thickness), various segments of the ring are measured separately. Morphologic changes (microcystic macular edema, epiretinal membranes, vitreoretinal traction, and photoreceptor atrophy) visible in the circular scan are assessed in the same way as in the macular scans.

Imaging modalities	Imaging equipment	Imaging software	Scan type	Parameters
SD-OCT	Spectralis HRA+OCT	Standard ophthalmology software	Optic nerve head scan	RNFL
			Volume scan	Retinal and GCL+IPL
SD-OCT	Spectralis HRA+OCT	Nsite software	Optic nerve head scan (ONHR-N)	RNFL
			Volume scan (PPoleN)	Retinal and GCL+IPL
SD-OCT	Cirrus HD-OCT		Optic disc cube scan	RNFL
			Macular cube scan	Retinal and GCL+IPL
			Cross hair scan	Not used

Nsite software and standard ophthalmology software modules used for image acquisition were part of the HRA2 / Spectralis Family Acquisition Module version 5.1.2.0 or higher. Image visualization and measurements were performed using the Heidelberg Eye Explorer Version 1.6.2.0 software.