ALZHEIMER'S DISEASE
Medical Imaging Expertise

BIOCLINICA

EXPERT INDEPENDENT IMAGE REVIEW
Board-certified Neuroradiologists assess image data for eligibility inclusion/exclusion criteria and safety findings. Centralized image review can significantly increase the efficiency of clinical trials while minimizing costs. Data are made available to sponsors in real-time enabling rapid patient monitoring and trial decisions.

SITE STANDARDIZATION and IMAGE QC
Bioclinica ensures high quality, reproducible MRI and PET data by minimizing site variability, providing vendor and model specific acquisition parameters, and ongoing quality control.

Magnetic Resonance Imaging (MRI)

MRI-based eligibility, safety, and efficacy endpoints play a key role in the design of AD clinical trials. Furthermore, the introduction of quantitative MRI endpoints and automated image processing enables high throughput analysis and adds valuable data in support of faster registrations.

Expertise in quantitative image processing for AD trials

- Freesurfer based cortical and subcortical segmentation
- Harmonized Hippocampus Protocol
- Longitudinal based measurements using Tensor Based Morphometry (TBM) and Boundary Shift Integral (BSI) for the assessment of global and regional atrophy
- Global, regional, and longitudinal changes in cortical thickness, including the Mayo AD signature ROI
- White-matter lesion volume
- Diffusion-Tensor Imaging (DTI) including Free-Water correction
- Magnetization Transfer Ratio (MTR)
- Arterial Spin Labeling (ASL) perfusion
- Resting-state and task-based fMRI

Positron Emission Tomography (PET)

Molecular imaging tracers used to visualize amyloid and tau proteins, and assess brain glucose metabolism provide key tools for identifying early disease.

PET Outcome Measures

- Tracer specific visual reads
- Standard Uptake Value Ratio (SUVr)
- FreeSurfer and template-based ROI methods
- Hybrid visual read with SUVr
- Distribution Volume Ratio
- Parametric voxelwise maps

Molecular Imaging Tracers

• FDG PET	• Amyloid PET	• Tau PET
• Investigational tracers	– Amyvid	– Tauvid
– F-DOPA	– Vizamyl	– MK6240
– TSPO	– Neuraceq	– PI2620
– SV2A	– PIB	– GTP1
	– NAV4694	

Site qualification and training

- Network of 800+ global PET imaging centers through 20+ countries worldwide
- On-site or virtual training
- Scanner performance assessed using Hoffman phantom
- Protocol set-up, validation and adherence
- Tracer handling and administration

Protocol Set-up and Site Qualification

MRI protocol will be designed in collaboration between Bioclinica scientists, neuroradiologists and Sponsor experts/KOLs. Bioclinica will interact with each study imaging site individually to deploy the MRI protocol consistently in a timely manner.

- Deployment across expert academic centers as well as standalone clinical imaging facilities
- Standardization across sites and optimization at each site
- Technologist web-based training (self-guided or remote)
- Site qualification including phantom scanning
- In-depth QC and feedback with fast turnaround

Advanced MRI

Diffusion Tensor Imaging (DTI)

DTI allows for the quantification of water displacement to access changes in white matter evolution as the result of therapeutic efficacy or continued neurodegeneration.

- Successful deployment at 500+ sites worldwide
- Standardized deployment of DTI protocols included reverse phase encode acquisitions for distortion correction
- 100% automated processing workflow that includes distortion correction, realignment, co-registration, and diffusion tensor estimation. Warping of derived maps to template space can also be implemented for regional, AD-specific statistics
- Multi-compartmental modeling of diffusion signal for estimation of free-water, a potential imaging biomarker sensitive to neuroinflammatory processes

PET Tracer Services

- Contract with PET tracer Contract Manufacturing Organizations (CMOs)
- Own communication between parties and develop plan to include agreed upon pathways of communication
- Facilitate regular meetings with Sponsor, CRO, and tracer CMOs to discuss imaging facility qualification, ordered/cancelled doses, and any issues or challenges
- Communicate PET imaging facility contact information to PET tracer CMOs
- Collect RAM license (or equivalent) from imaging facility to provide to PET tracer CMO
- Validate invoices submitted by PET tracer CMO against scans collected for the study

PET Imaging within the NIA-AA ATN framework

Bioclinica supports PET imaging biomarkers which can non-invasively measure β amyloid deposition (A), pathologic tau (T), neurodegeneration (N) and other categories beyond ATN such as inflammation.

Amyloid PET (A)

- Visual reading methods follow the criteria established by the selected amyloid tracer's methodology for visual assessment. Bioclinica's readers are certified in all three 18F amyloid tracers that have been approved in the USA and EU.
- SUVr is the most common semi-quantitative measure to assess amyloid burden in multicenter clinical trials. SUVr can be computed for global cortical composites as well as individual regions in both native and template spaces. All tracer-recommended reference regions are available.

Functional MRI (fMRI)

FMRI detects the blood oxygen level–dependent changes in the MRI signal that arise when changes in neuronal activity occur following a change in brain state, at rest from spontaneous activity or induced by a stimulus or task.

- Successful deployment at 1300+ sites worldwide
- 100% automated preprocessing stream including motion correction, distortion correction, registration to anatomical space, segmentation, and parcellation
- For resting-state fMRI, the complete connectivity matrix reports functional relationships between all brain regions (seed-based and ICA approaches also possible). Amplitude of low frequency fluctuations may be quantified using the f/ALFF metric.
- For task-based fMRI, General Linear Models (containing predictors of interest and nuisance regressors) are estimated to derive the effects of a task

Arterial Spin Labeling (ASL) Perfusion

ASL assesses changes in cerebral blood flow (CBF) in a non-invasive manner, potentially reflecting hyper/hypo-metabolism traditionally investigated with FDG PET.

- Successful deployment at 300+ sites worldwide
- Facilitate installation of state-of-the-art C2P 3D PCASL
- 100% automated preprocessing stream including co-registration, subtraction, denoising, CBF calculation, registration to anatomical space, segmentation, and parcellation
- CBF calculation over the whole brain as well as over AD-specific composite ROIs to maximize sensitivity

Tau PET (T)

- Visual reads: Bioclinica provides CFR part 11 compliant visual reading systems for all second-generation tau tracers. Bioclinica has adapted its PET image preprocessing pipeline to best suit the characteristics of tau images. The current processing pipeline includes motion correction, smoothing to a uniform spatial resolution across all scanner models, registration of PET to MRI in common template space to allow a consistent data presentation with both tau and anatomical information available.
- Regional SUVR values are computed for the entire FreeSurfer parcellation, allowing inspection of relevant a priori targets (hippocampus, parahippocampus, fusiform gyrus, amygdala, etc.), composites (medial, lateral temporal and parietal lobes) and subject-specific sites of maximal uptake. The full spectrum of Braak-stage and MeTeR areas can also be derived.
- Partial Volume Correction with different methods adjusted to tracer characteristics and reference region is also available.
- If desired, Bioclinica neuroradiologists can make use of SUVr information to supplement their visual read (hybrid read).

FDG and SV2A PET (N)

- FDG: In addition to visual reads, global and regional ROI-based analyses, Bioclinica supports whole brain Metabolic Rate of Glucose (MRGlu) maps, metabolic influx (Ki) maps, Distribution volume Ratios (DVR) and statistical ROI analysis (sROI) within AD-spared and decline regions.
- For novel PET tracers such as SV2A (UCB-A, UCB-H and UCB-J) Bioclinica offers a suite for absolute quantification, including dynamic PET acquisition (protocol set-up, standardization and validation), blood sampling standardization, kinetic analysis and modeling.