

Biomarker Recommendations for GBA1 Therapeutic Trials in Parkinson's Disease

This document provides biomarker guidance for sponsors and investigators designing clinical trials targeting GBA1, including small-molecule GCase activators and pharmacological chaperones, substrate reduction therapies, enzyme replacement, and gene therapy, in Parkinson's Disease (PD). Although not necessarily meant to be prescriptive, this document reflects emerging clinical trial data, current assay availability, and input from external advisors. Recommendations address GBA1 variant carriers and, where relevant, idiopathic PD enrollment strategies. Biomarkers are organized by mechanistic proximity to GBA1: direct pharmacodynamic or target engagement markers, downstream pathway engagement markers (not specific to GCase activation but often used as target engagement / pharmacodynamic markers), neurodegeneration / disease pathology biomarkers and discovery / exploratory biomarkers for Phase 1 and Phase 2 clinical trials. Predictive markers or those with enrichment potential include presence of a GBA1 genetic variant or evidence of lysosomal dysfunction (e.g. elevated urine BMP).

Recommended Tiered Biomarker Panel

Compartment	C	CSF	P	PLASMA	B	DRY BLOOD SPOT	U	URINE	L	PBMC
DIRECT Target Engagement / Pharmacodynamic Biomarkers DOWNSTREAM Pathway Modulation / Pharmacodynamic Biomarkers NEURODEGENERATION Stratification / Disease Pathology Biomarkers										
GCase activity	C	P	B	L						
GluSph	C	P	B							
GluCer	C	P	U							
BMP			P	U						
Targeted lipid multiplex panel	C	P	U							
Lysosomal multiplex panel	C									
NfL	C	P								
GFAP		P								
α-Synuclein (total/pS129/SAA)	C									
Aβ42 / Aβ40	C	P								
Tau (p-tau181, p-tau217, MTBR-tau243)	C	P								

Discovery platforms for additional exploratory measures: Proteomics in CSF & plasma (NULISA, Olink), metabolomics in CSF, plasma & urine (Metabolon), untargeted lipidomics in CSF, plasma & urine (Ardena, Lipotype, Nextcea)

Biomarker Reference Table

Category	Biomarker/Compartment	Platform (Source)	Assay Status / Findings
Direct measures	GCase enzymatic activity / CSF, plasma, PBMC, dry blood spot	Mass spectrometry & fluorimetry (Nextcea, Revvity, Centogene)	Reduced in GBA1 carriers with severity-dependent decline ^{1,2} ; CSF activity reduced in PD irrespective of GBA1 status ³ . Dry blood spot harmonization round-robin ongoing. Sustained GCase activation (>50%) shown in Ph1 of VQ-101 via live-cell assay ⁴ .

Direct measures	Glucosylsphingosine (GluSph) / CSF, plasma, dry blood spot	Mass spectrometry (Ardena, Nextcea, Lipotype, Centogene; Denali, Merck)	Elevated in plasma of GBA1 carriers irrespective of PD status ^{5,6} ; CSF GluSph is a central readout of GCase impairment across genetic and sporadic PD ⁷ with reduction reported after GT-02287 (Ph1b) ⁸ . CSF round-robin ongoing. Plasma/CSF correlation is limited.
Direct measures	Glucosylceramide (GluCer species- 16:0, 18:0, 20:0, 22:0, 22:1, 23:0, 24:0, 24:1, 24:2, 26:0, 26:1) / CSF, plasma, urine	Mass spectrometry (Nextcea, Lipotype, Denali, Escape Bio, Sanofi)	CSF GluCer:sphingomyelin ratio elevated in GBA-PD from PPMI ⁹ ; plasma GluCer proposed as pharmacodynamic biomarker ¹⁰ . Divergent GluSph vs GluCer behavior not fully understood.
Downstream measures	Targeted lipid panels (GluSph/GalSph, BMP, ceramides, gangliosides, GluCer/GalCer, Cer-1, sphingosines, Lyso-Gb3) / CSF, plasma, urine	Mass spectrometry (Nextcea, Lipotype)	PPMI data generation ongoing (expected Q1 2027) ¹⁶ . CSF testing in PPMI contingent on plasma/urine assessments. CSF d18:1 sphingolipid species unchanged in heterozygous GBA1 carriers ¹¹ .
Downstream measures	BMP (18:0_16:0, 18:0_18:0, 18:1_16:0, 18:1_16:1, 18:1_18:1, 18:1_18:2, 18:1_20:1, 18:1_20:2, 18:1_20:3, 18:1_20:4, 18:1_22:6, 18:2_16:0, 18:2_18:0, 20:1_22:6, 20:4_16:0, 20:4_18:0, 20:4_20:4, 20:4_22:6, 22:6_22:6) / urine, plasma	Mass spectrometry (Nextcea, Lipotype)	Urinary BMP elevated 30-40% in GBA1 variant carriers in PPMI ^{12,13} ; normalize to creatinine. Use as predictive/ pharmacodynamic marker only; prognostic use did not qualify ¹³ .
Downstream measures	Lysosomal protein panel (CTSB/D/F/L/S, GPNMB, GM2A, LAMP1/2, LC3, ubiquitin, GCase) / CSF, plasma	Mass spectrometry (Biogen; broader panel including other endolysosomal markers at Inoviv, Biognosys, University of Gothenburg)	Data generation ongoing in the Brockmann GBA1 CSF cohort across the variant-severity spectrum. GPNMB is a secreted marker of lysosomal dysfunction ¹⁴ . Biogen CSF panel data available in PPMI via LONI ¹⁶ , identifying a lysosomal PD signature relevant for subtyping & patient stratification.
Neurodegeneration	α -Syn (SAA/total/pS129) / CSF	SAA (Amprion), Total/pS129: Immunoassay (MSD, SIMOA (Quanterix), Elecsys (Roche)	GBA1-PD predominantly SAA-positive ¹⁵ ; recommended for cohort stratification, not as a pharmacodynamic readout. Total/pS129: short trials unlikely to show change; include for stratification.
Neurodegeneration	NfL / CSF, plasma	SIMOA (Quanterix, NCRAD)	PPMI data available via LONI ¹⁶ ; axonal injury marker used in exploratory manner for progression and as prognostic for cognitive decline in PD.



Neurodegeneration	GFAP / plasma	SIMOA (Quanterix, NCRAD)	PPMI data available via LONI ¹⁶ ; exploratory marker for astrogliosis.
Neurodegeneration	Aβ42/40 / CSF, plasma	CSF: Lumipulse (Fujirebio); plasma: Precivity (C2N, NCRAD)	Co-pathology marker; relevant to cognitive stratification in GBA-PD. PPMI data indicate baseline levels prognostic for future cognitive decline ¹⁶ .
Neurodegeneration	p-tau181, p-tau217, MTBR-tau243 / CSF, plasma	CSF (Fujirebio); plasma (C2N, Lilly, NCRAD)	Co-pathology markers; relevant to cognitive stratification in GBA-PD. PPMI data indicate baseline levels prognostic for future cognitive decline ¹⁶ .
Discovery platform	Proteomics / CSF, plasma	NULISA (Alamar), Olink	PPMI data available via LONI, data analysis ongoing ¹⁶
Discovery platform	Untargeted lipidomics / CSF, plasma, urine	Ardena, Lipotype, Nextcea	PPMI data generation ongoing (expected Q1 2027) ¹⁶ . CSF testing in PPMI contingent on plasma/urine assessments.
Discovery platform	Metabolomics / CSF, plasma, urine	Metabolon	PPMI data available Q4 2026 via LONI ¹⁶

Additional notes

- Validated clinical scales should be included in all trials to contextualize biomarker changes against functional outcomes. MDS-UPDRS remains the standard clinical outcome measure; the ACTIVATE Ph2b primary endpoint was time to clinically meaningful motor progression (MDS-UPDRS Parts II–III)¹⁷. Given the elevated cognitive risk in GBA-PD, recommend including cognitive measures (e.g., MoCA) and consider amyloid/tau co-pathology stratification. ACTIVATE did not meet its primary endpoint (topline, June 2026)¹⁷, reinforcing the need for biomarker-guided enrichment and confirmed target engagement.
- GluSph interpretation: plasma GluSph is elevated in GBA1 carriers irrespective of PD status^{5,6}, with some conflicting data for mild variants (e.g., N409S)¹⁸. Absolute CSF values differ across CROs and plasma-CSF correlation is limited; use a single platform/CRO within a trial.
- GCase activity assays differ in substrate, cell type, CBE inhibition and live-cell requirements, and most provide only relative quantification. Thresholds for clinically meaningful change are not established, though the ongoing round-robin in dried blood spots (readout Q4 2026) aims to recommend platforms and enable cross-program comparison.
- Mass spectrometry (Nextcea, Lipotype) is preferred for lipid analytes; SIMOA (Quanterix/ADx) or other ultrasensitive platforms are preferred for low-abundance proteins. All assays should be performed in CLIA-certified or equivalent labs with pre-defined QC criteria.
- PBMC and live-cell GCase assays are sensitive to sample processing time and may require fresh samples; standardize collection protocols and collection-to-freezing intervals across sites.
- Assays in development:
 - Imaging modalities in early development: LysoCEST MRI of GluCer/intralysosomal pH, GCase PET tracer
 - Cathepsin B activity assay (developed by Vanqua Bio) measured via flow cytometry in monocytes & PBMCs currently being optimized utilizing several cohorts around the world (BioFIND, BIOPARK, Hospital of Bordeaux) being developed for monocytes & PBMCs



References

1. Alcalay RN, et al. Glucocerebrosidase activity in Parkinson's disease with and without GBA mutations. *Brain* 2015. <https://doi.org/10.1093/brain/awv179>
2. Huh YE, et al. β -Glucocerebrosidase activity in GBA-linked Parkinson disease. *Neurology* 2020. <https://doi.org/10.1212/WNL.0000000000009989>
3. Parnetti L, et al. Cerebrospinal fluid β -glucocerebrosidase activity is reduced in Parkinson's disease patients. *Mov Disord* 2017. <https://doi.org/10.1002/mds.27136>
4. Facheris M, et al. VQ-101, a CNS-penetrant small molecule allosteric activator of glucocerebrosidase (GCase), demonstrates favorable tolerability and sustained activation of lysosomal GCase in individuals with Parkinson's disease. *MDS Abstracts* 2025. <https://www.mdsabstracts.org/abstract/vq-101-a-cns-penetrant-small-molecule-allosteric-activator-of-glucocerebrosidase-gcase-demonstrates-favorable-tolerability-and-sustained-activation-of-lysosomal-gcase-in-individuals-with-parkinson/>
5. Surface M, et al. Plasma glucosylsphingosine in GBA1 mutation carriers with and without Parkinson's disease. *Mov Disord* 2021. <https://doi.org/10.1002/mds.28846>
6. Agin-Lieb J, et al. Plasma glucosylsphingosine in GBA1 E365K, N409S, and L483P heterozygous mutation carriers. *Mov Disord* 2026. <https://doi.org/10.1002/mds.70205>
7. Kluss JH, et al. CSF glucosylsphingosine is a central readout of GCase impairment across genetic and sporadic Parkinson's disease. *bioRxiv* 2026. <https://doi.org/10.64898/2026.06.19.733447>
8. Gain Therapeutics. Gain Therapeutics receives FDA clearance of IND to advance GT-02287 into Phase 2 clinical development for Parkinson's disease. Press release, June 29, 2026. <https://gaintherapeutics.com/newsroom/press-releases/press-releases-2026/gain-therapeutics-receives-fda-clearance-of-ind-to-advance-gt-02287-into-phase-2-clinical-development-for-parkinsons-disease/>
9. Huh YE, et al. Glucosylceramide in cerebrospinal fluid of patients with GBA-associated and idiopathic Parkinson's disease enrolled in PPMI. *npj Parkinsons Dis* 2021. <https://doi.org/10.1038/s41531-021-00241-3>
10. den Heijer JM, et al. A biomarker study in patients with GBA1-Parkinson's disease and healthy controls. *Mov Disord* 2023. <https://doi.org/10.1002/mds.29360>
11. Lerche S, et al. CSF d18:1 sphingolipid species in Parkinson disease and dementia with Lewy bodies with and without GBA1 variants. *npj Parkinsons Dis* 2024. <https://doi.org/10.1038/s41531-024-00820-0>
12. Alcalay RN, et al. Higher urine bis(monoacylglycerol)phosphate levels in LRRK2 G2019S mutation carriers: implications for therapeutic development. *Mov Disord* 2019. <https://doi.org/10.1002/mds.27818>
13. Merchant KM, et al. LRRK2 and GBA1 variant carriers have higher urinary bis(monoacylglycerol)phosphate concentrations in PPMI cohorts. *npj Parkinsons Dis* 2023. <https://doi.org/10.1038/s41531-023-00468-2>
14. Bogacki EC, et al. GPNMB is a biomarker for lysosomal dysfunction and is secreted via LRRK2-modulated lysosomal exocytosis. *Sci Adv* 2025. <https://doi.org/10.1126/sciadv.adv1434>
15. Fraser KB, et al. Analysis of α -synuclein seed amplification assay in carriers of GBA1 and LRRK2 pathogenic variants. *J Parkinsons Dis* 2026. <https://doi.org/10.1177/1877718x251392799>
16. Parkinson's Progression Markers Initiative (PPMI) data, accessed via LONI: <https://www.ppmi-info.org/access-data-specimens/download-data>
17. Alzforum Therapeutics: BIA 28-6156 (pariceract; ACTIVATE Phase 2b topline, June 2026). <https://www.alzforum.org/therapeutics/bia-28-6156>
18. Gleason A, et al. No evidence that glucosylsphingosine is a biomarker for Parkinson's disease: statistical differences do not necessarily indicate biological significance. *Mov Disord* 2022. <https://doi.org/10.1002/mds.28935>

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