Longitudinal 18F-PBR06 (TSPO) and Volumetric MR Imaging as Pharmacodynamic Endpoints for MSA – Ongoing Investigator-Sponsored Trial of Verdiperstat

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Background: Clinical trials in neurodegenerative diseases may be doomed to fail because patient populations are heterogeneous and a "one size fits all" strategy may not work. Second, clinical endpoints may be too crude to monitor efficacy. A Phase 3 trial for one such disease, multiple system atrophy (MSA), was just completed (09/2021); it found no significant impact of verdiperstat compared to placebo (NCT03952806) with respect to primary clinical endpoints. Yet, it is known that neuroinflammation and focal cerebral volume loss are hallmarks of MSA and track with clinical subtypes. These can be measured *in vivo* with ^{18}F-PBR06, a second-generation PET-translocator protein (TSPO) radioligand for assessment of cerebral microglial activation[1], and 3D-MRI volumetric segmentation[2], respectively. Here, in well characterized patients, we dissect pharmacodynamic engagement of this drug through brain imaging.

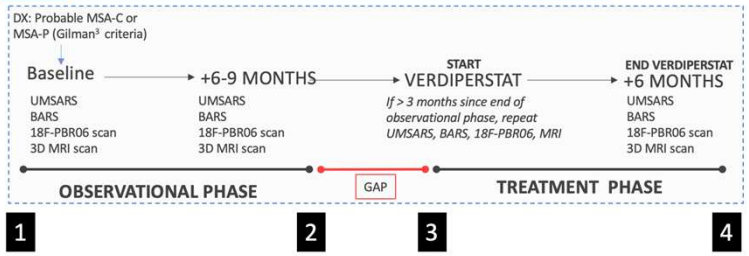
Objectives: In MSA patients to: 1) evaluate ^{18}F-PBR06 PET for longitudinal assessment of 18-kilodalton-TSPO binding; 2) assess relationship of ^{18}F-PBR06 with clinical parameters and fully automated 3D-MRI volumetric segmentation of defined brain regions; and 3) determine pharmacodynamic effects of verdiperstat, an orally administered myeloperoxidase inhibitor.

Methodology: 21 patients with clinically probable MSA-P(parkinsonian)/MSA-C(cerebellar) are enrolled (NCT04616456; Fig. 1) ***Trial Design*** *Observational Phase*: At entry and after 6-9 months, patients undergo clinical assessments (Unified MSA Rating Scale [UMSARS] and Brief Ataxia Rating Scale [BARS]) and imaging analysis (^{18}F-PBR06 and 3D-MRI). Biospecimens—blood, stool, skin biopsies, and CSF—are also collected. ***Treatment Phase*:** Patients are treated with verdiperstat 600-mg twice daily for six months. At the end of this period, clinical, ^{18}F-PBR06, MRI, and biospecimens are re-obtained (Fig. 2). ***Observation Phase Exemption:*** 7 patients transitioned directly into the Treatment Phase based on evidence of rapid progression at presentation, including loss of ambulation in ≤1 year previous year and ≥1 UMSARS global disability scale decrease in ≤6 months. ***Imaging*:** Assessment of MRI and ^{18}F-PBR06 is separate and blinded. Standardized Uptake Value Ratios (SUVRs) are normalized to global brain SUV for PET. FreeSurfer automates volumetric segmentation of high-resolution isotropic T1 MRIs.

	MSA-03	MSA-04	MSA-05	MSA-07	MSA-09	MSA-17	15 Additional Subjects
Age At Study Start (years)	52	74	61	57	78	48	56-83 (M: 70.1, SD: 9.1)
Legal Sex	Female	Female	Female	Male	Male	Female	10 Male 5 Female
Diagnosis (probable)	MSA-C	MSA-C/P	MSA-C	MSA-P	MSA-C	MSA-C	
Symptom Onset	c. 2014	c. 2008	c. 2012	c. 2015	c. 2019	c. 2019	
Supportive Testing	FDG-PET Skin Biopsy	FDG-PET SCA2/3 genetics	FDG-PET	FDG-PET	FDG-PET Autonomic testing	SCA 1/2 genetics	7 Dx: MSA-C 7 Dx: MSA-P 1 Dx: MSA-C/P
Chief Complaint	Orthostatic hypotension	REM Behavior Disorder (RBD), dream re-enactment	Urinary incontinence, dream re-enactment, tremor	Lateralized bradykinesia and action tremor	Cerebellar speech, incoordination	Dream re-enactment, orthostatic hypotension	

Figure 1: Study participant profiles

Figure 2: Clinical trial design



Preliminary Results: We report here on preliminary PET, MRI, and clinical data from 6 patients: 3 presented with progressive motor/autonomic symptoms (MSA-03/05/07/09/17); the fourth presented with REM behavior disorder on polysomnography (RBD; MSA-04) and was found to have mild ataxia-parkinsonism on examination. 2 have completed treatment with verdiperstat (MSA-03/07).

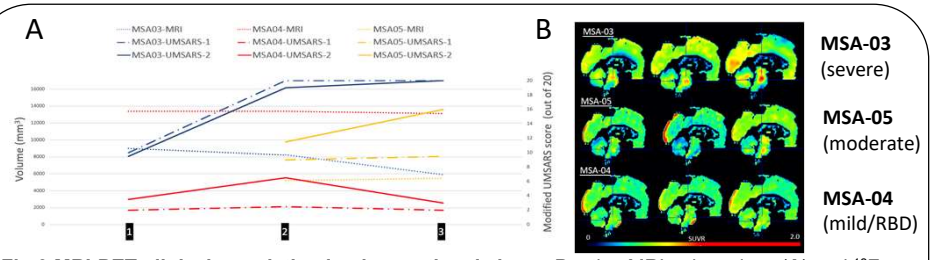


Fig.3 MRI-PET-clinical correlation in observational phase: Pontine MRI volume loss (**A**) and ^{18}F-PBR06 signal (B) correlated with clinical deterioration, as measured by UMSARS. Note that the MRI and PET signal remained unchanged in MSA-04, consistent with her stable clinical status.

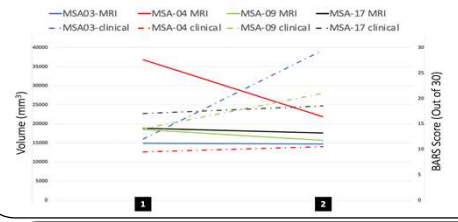


Fig. 4 MRI-clinical correlation in observational phase: Cerebellar White Matter volume correlated with clinical deterioration [BARS scale]. In this case, volume loss was also noted in MSA-04, the mild case who presented with RBD, but the absolute value of the volume remained above that of the other subjects and this subject did not exhibit progressive worsening of ataxia clinically.

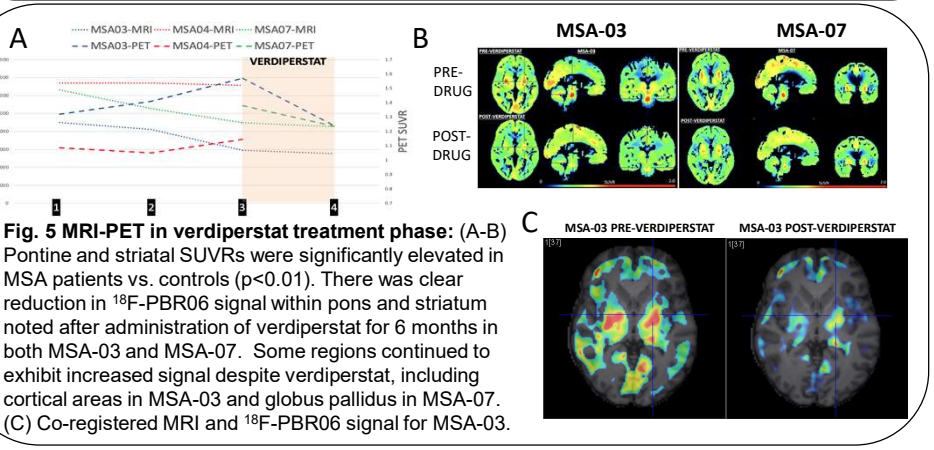


Fig. 5 MRI-PET in verdiperstat treatment phase: (A-B) Pontine and striatal SUVRs were significantly elevated in MSA patients vs. controls ($p<0.01$). There was clear reduction in ^{18}F-PBR06 signal within pons and striatum noted after administration of verdiperstat for 6 months in both MSA-03 and MSA-07. Some regions continued to exhibit increased signal despite verdiperstat, including cortical areas in MSA-03 and globus pallidus in MSA-07. (C) Co-registered MRI and ^{18}F-PBR06 signal for MSA-03.

Conclusions: Tracking structural brain alterations with 3D-volumetric MRI or neuroinflammation with ^{18}F-PBR06 PET-TSPO imaging correlate with (and may outperform) clinical rating scales as MSA progresses over ≥6 months. In the two patients who completed 6 months of verdiperstat, there was clear reduction in TSPO signal in pons and most deep gray matter structures. TSPO signal in some brain regions continued to increase after verdiperstat treatment. We await more definitive data as this clinical trial reaches completion.

References: 1) *J Nucl Med* 2009;50(7):1047-53. 2) *Neurology*. 2016;86(13):1242-9. 3) *Neurology*. 2008;71(9):670-676.

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