PD-1102: A Phase 1 Study of VY-AADC01 Administered Using a Posterior Approach in Patients with Parkinson's Disease and Motor Fluctuations

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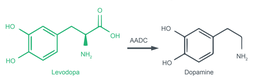
Introduction

- Progression of Parkinson's disease (PD) leads to loss of L-amino acid decarboxylase (AADC), which limits levodopa efficacy[1-3]
  - Results in motor fluctuations and troublesome dyskinesias



- In MPTP-lesioned non-human primates, 35% coverage of striatum by infused adeno-associated viral vector serotype-2 (AAV2)-AADC was associated with durably enhanced levodopa response[4]
- In PD patients, early phase 1 studies of AAV2-AADC delivered to bilateral putamen showed durable AADC enzyme activity[5,6]
  - Small infusion volumes may have limited clinical benefit
- Phase 1b study (PD-1101) in PD patients used a novel intraoperative MRI procedure to administer VY-AADC01 (AAV2-AADC) to bilateral putamen[7]
  - Frontal approach requiring two or more trajectories per putamen
  - Infusion volumes up to 900 µL/putamen resulted in mean putaminal coverage of 42%
  - Dose-related improvements in measures of motor function and quality of life (QoL); no vector-related serious adverse events (AEs) reported to date

Objectives

- Present results from phase 1 study PD-1102 (NCT03065192)
  - VY-AADC01 infused via posterior trajectory; infusion volumes up to 1800 µL/putamen
- Determine percentage of putaminal coverage by VY-AADC01 (target ≥50%)
- Assess putaminal AADC enzyme activity by (18)F-fluoro-L-dihydroxyphenylalanine (^{18}F-DOPA) PET
- Assess safety and clinical response at 12 months

Methods

Study design

- Single-arm, open-label, phase 1 study of VY-AADC01 in patients with PD using posterior approach **(Figure 1)**

Figure 1. PD-1102 study design

Key Entry Criteria
- Advanced PD with disabling motor fluctuations despite optimal medical therapy
- Disease duration ≥5 years
- History of responsiveness to dopaminergic therapy

PD-1102 (N = 8)

Surgical approach	Volume per putamen	Concentration	Total dose
Posterior	Up to 1800 µL	Up to 2.6×10^{12} vg/mL[a]	Up to 9.4×10^{12} vg[a]

12-month follow-up

Key Endpoints
- Safety
- Putaminal coverage
- AADC enzyme activity in the putamen by ^{18}F-DOPA PET
- Levodopa and related medications requirements
- ON and OFF times per patient-reported diaries
- Unified Parkinson's Disease Rating Scale (UPDRS) on and off medication
- QoL

[a]Based on data from the ongoing PD-1101 study, one of the eight patients in PD-1102 received a lower vector genome (vg) concentration of 8.3×10^{11} vg/mL, equivalent to cohort 2 in PD-1101. This vg concentration was consistent with the PD-1102 protocol and was not due to safety concerns.

VY-AADC01 infusion and putaminal coverage

- ClearPoint® neuro-navigational system (MRI Interventions, Inc., Irvine, CA) used for delivery
- VY-AADC01 admixed with gadoteridol (1–2 mM) infused using convection-enhanced delivery and intraoperative MRI[8,9]
  - Single posterior (parietal-occipital) trajectory per putamen to improve delivery to postcommissural putamen
  - iPlan Flow software (Brainlab AG, Munich, Germany) used to analyze distribution

AADC enzyme activity

- ^{18}F-DOPA PET before and 2–7 months after VY-AADC01 infusion
  - Striatum (putamen) to occipital cortex standardized uptake value ratio (SOR-1) calculated and expressed as change from baseline[7,10]

Clinical assessments

- AEs and serious AEs
- Antiparkinsonian medications, standardized to levodopa-equivalent dose (LED)[11,12]
  - LED adjusted for dyskinesias, other side effects of dopaminergic medications, or reduced need
- Patient-completed Hauser diaries (averaged over 3 consecutive days)
- Clinician-assessed outcomes:
  - UPDRS Part III on and off medication
  - Clinical Global Impression of Change (CGI-C)
- Patient-reported outcomes:
  - 39-item Parkinson's Disease Questionnaire (PDQ-39, a QoL assessment)
  - Patients' Global Impression of Change (PGI-C)
- All data reported as mean ± standard error of the mean (SEM) unless indicated

Subgroup analyses

- Exploratory analyses in PD-1101 suggested patients with high dyskinesia or impulse control disorder (ICD) at baseline may show different outcomes, especially in patient-reported diary measures
- All clinical assessments analyzed for two exploratory subgroups
  - Dys/ICD(-) subgroup: no or low baseline dyskinesia (Unified Dyskinesia Rating Scale [UDysRS] score ≤30) and absence of ICD at baseline (determined by investigator)
  - Dys/ICD(+) subgroup: high baseline dyskinesia or ICD at baseline

Results

Baseline characteristics

- Among the eight enrolled patients:
  - Two had high dyskinesia (UDysRS score >30)
  - Two had ICD as determined by investigator

Table 1. Demographic and baseline characteristics

	Total (N = 8)	Dys/ICD(-) (n = 4)	Dys/ICD(+) (n = 4)
Age, y	56.8 (3.9)	58.5 (6.3)	55.0 (5.4)
Male, n (%)	7 (87.5)	3 (75.0)	4 (100)
Duration of PD, y	9.2 (2.1)	8.2 (2.6)	10.1 (3.6)
UPDRS II off medication	15.3 (2.1)	15.0 (1.7)	15.5 (4.2)
UPDRS II on medication	3.5 (1.5)	3.0 (1.3)	4.0 (3.0)
UPDRS III off medication	34.9 (1.8)	36.3 (2.8)	33.5 (2.6)
UPDRS III on medication	11.4 (2.1)	13.8 (3.0)	9.0 (2.8)
Hauser diary OFF time, h	6.8 (0.6)	7.2 (0.8)	6.4 (0.8)
Hauser diary good ON time, h[a]	9.1 (0.5)	8.8 (0.8)	9.4 (0.8)
Modified Hoehn and Yahr scale, n			
Stage 2.5	4	0	4
Stage 3	4	4	0
UDysRS, total score	22.8 (4.8)	16.0 (5.4)	29.5 (7.1)
Baseline LED, mg	1500.9 (179.2)	1187.9 (144.8)	1813.9 (252.3)

Data are mean (standard error). Hauser diary data normalized to a 16-hour day.
[a]Refers to ON time without dyskinesia + ON time with non-troublesome dyskinesia.
Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

Safety

- No serious AEs reported **(Table 2)**
- Two grade 1 intraoperative intracerebral hemorrhages reported
  - One patient had subtle visual disturbance; fully resolved
  - One patient asymptomatic
  - Infusion procedures continued as planned; no change in hemorrhage volume observed during infusion
- Transient increases in dyskinesia reported in two patients
- Worsening of ICD (hypersexuality) reported in one patient in Dys/ICD(+) subgroup

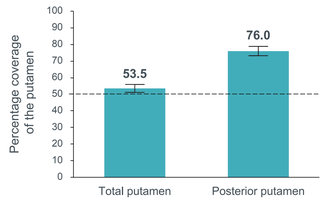
Table 2. Treatment-emergent AEs reported in ≥2 patients in any organ class

System organ class and preferred term	Total (N = 8), n (%)
Patients experiencing ≥1 AE	7 (87.5)
Gastrointestinal	
Constipation	2 (25.0)
Nausea	2 (25.0)
Nervous system	
Headache	3 (37.5)
Dyskinesia	2 (25.0)
Infections and infestations	
Upper respiratory tract infection	3 (37.5)
Musculoskeletal and connective tissue	
Musculoskeletal chest pain	2 (25.0)

Putaminal coverage, AADC enzyme activity, and LED changes

- Despite greater infusion volume (≤1800 µL vs ≤900 µL in PD-1101 cohort 3), infusion time was reduced from 5.2 hours to 3.1 hours
- Total putaminal coverage exceeded 50% target **(Figure 2)**
- AADC enzyme activity increased 84.9% from baseline
- LED reduced by 27.6 ± 4.5% (417 mg) 6 months post VY-AADC01; maintained at 12 months

Figure 2. Coverage of the putamen and AADC enzyme activity



AADC enzyme activity (^{18}F-DOPA PET) increase from baseline:

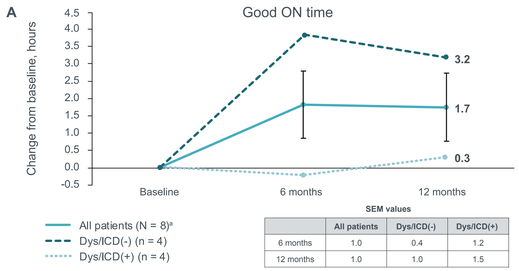
84.9 ± 10.0%[a]

Imaging frames captured 65–75 minutes after ^{18}F-DOPA administration.
[a]n = 7. One patient (24.1% difference from baseline) excluded due to movement artifact during scan. PET change was 77.3 ± 11.5% for all patients (N = 8).

Clinical efficacy

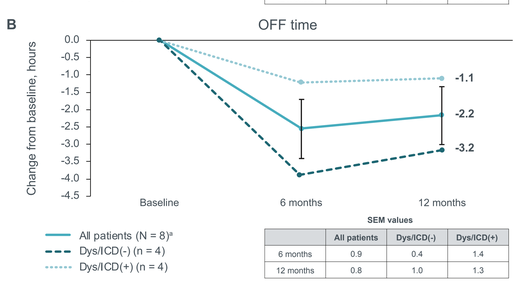
- At 12 months, 1.7-hour increase in good ON time (ON time without dyskinesia + ON time with non-troublesome dyskinesia) and 2.2-hour decrease in OFF time from baseline **(Figure 3)**
  - Dys/ICD(-) subgroup: 3.2-hour increase in good ON time and 3.2-hour decrease in OFF time from baseline

Figure 3. Change from baseline in diary (A) good ON and (B) OFF time normalized to 16-hour waking day



SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	1.0	0.4	1.2
12 months	1.0	1.0	1.5



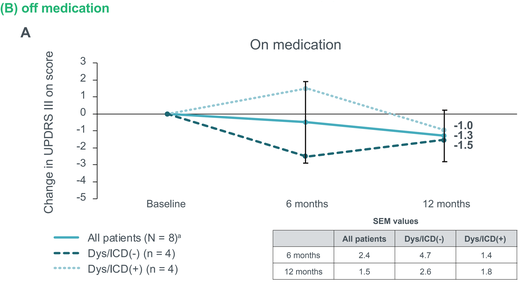
SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	0.9	0.4	1.4
12 months	0.8	1.0	1.3

[a]Excluding patient who received lower vg concentration, change in good ON time 1.4 ± 1.1 hours and OFF time -1.9 ± 0.9 hours at 12 months.
Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

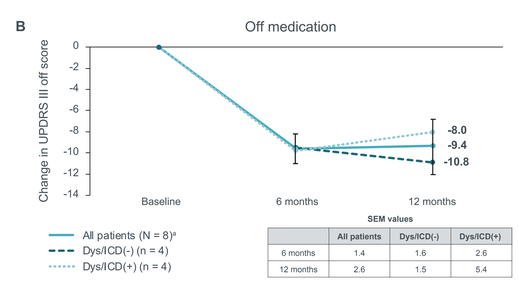
- At 12 months, clinically meaningful[13] improvement (reduction) in UPDRS III scores off medication and minor change in UPDRS III scores on medication **(Figure 4)**

Figure 4. Change from baseline in UPDRS III scores (A) on medication and (B) off medication



SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	2.4	4.7	1.4
12 months	1.5	2.6	1.8



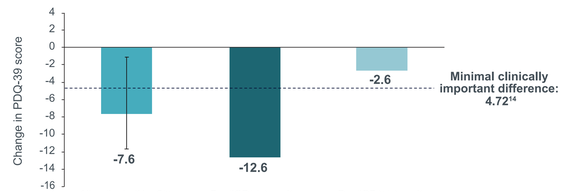
SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	1.4	1.6	2.6
12 months	2.6	1.5	5.4

[a]Excluding patient who received lower vg concentration, change in UPDRS III score on medication -2.3 ± 1.2 and off medication -9.3 ± 3.0 at 12 months.
Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

- At 12 months, PDQ-39 score reduced from baseline, indicating improved QoL **(Figure 5)**
  - Greater improvements in Dys/ICD(-) subgroup

Figure 5. Change from baseline in PDQ-39 score 12 months post VY-AADC01



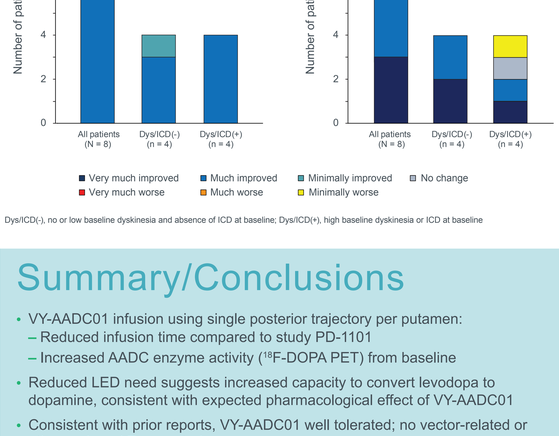
SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
12 months	4.8	3.6	8.9

[a]Excluding patient who received lower vg concentration, change in PDQ-39 score -6.2 ± 5.3 at 12 months.
Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

- Clinicians reported improvement in clinical status in all patients at 12 months **(Figure 6)**
- Six of eight patients reported improvement at 12 months
  - Dys/ICD(-) subgroup: all patients reported improvement
  - Dys/ICD(+) subgroup: one patient reported no change (high baseline dyskinesia) and one reported minimal worsening (ICD)

Figure 6. Clinician- and patient-reported impression 12 months post VY-AADC01



Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

Summary/Conclusions

- VY-AADC01 infusion using single posterior trajectory per putamen:
  - Reduced infusion time compared to study PD-1101
  - Increased AADC enzyme activity (^{18}F-DOPA PET) from baseline
- Reduced LED need suggests increased capacity to convert levodopa to dopamine, consistent with expected pharmacological effect of VY-AADC01
- Consistent with prior reports, VY-AADC01 well tolerated; no vector-related or other serious AEs reported
- At 12 months, improvements in clinician- and patient-reported outcomes:
  - Increase in good ON time and decrease in OFF time
  - Improved UPDRS III off medication
  - Improved patient-reported QoL
  - Improved clinical status (CGI-C)
- Exploratory subgroup analyses suggest that patients with high baseline dyskinesia (UDysRS >30) or preexisting ICD show different outcomes
- A randomized, placebo surgery-controlled, double-blind, phase 2 trial to evaluate VY-AADC02 in patients with PD and medically refractory motor fluctuations is ongoing (RESTORE-1; PD-1105; NCT03562494)

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Acknowledgments We thank the patients and their families who participated in this trial. Financial support for this trial and trial materials were provided by The Michael J. Fox Foundation to KSB and PSL and by Voyager Therapeutics, Inc. Medical writing and editorial support were provided by Ward A. Pedersen, PhD, and Shannon Davis of Ashfield Healthcare Communications, Middletown, CT, and funded by Voyager Therapeutics, Inc. **Disclosures ADVL, CWC, and SAF receive research support from The Michael J. Fox Foundation and Voyager Therapeutics, Inc. RMR and PSL receive research support from Voyager Therapeutics, Inc., and personally receives compensation for these services. SKK has nothing to disclose. RL receives consulting fees from Voyager Therapeutics, Inc. AS is an employee of, and owns stock in, Voyager Therapeutics, Inc. BR is a former employee of Voyager Therapeutics, Inc., and is now employed by Praxis Precision Medicines, Inc., and has a patent pending on *AADC* gene transfer in Parkinson's disease. AK is a former employee of, and owns stock in, Voyager Therapeutics, Inc., and is now employed by Brain Neurotherapy Bio, Inc. KSB receives research support and consulting fees from, and owns stock in, Voyager Therapeutics, Inc., and has intellectual property rights to VY-AADC01.**

Presented at the Annual Meeting of the American Academy of Neurology | May 4–10, 2019 | Philadelphia, Pennsylvania