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Comparative evaluation of active and passive immunization therapy strategies targeting toxic forms of α-synuclein in Parkinson's disease patient brain: UB-312 vaccine vs. ABBV-0805 antibodies

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ABSTRACT

Progressive neurodegeneration and toxic α-synuclein aggregation are features of Parkinson's disease. Immunotherapy targeting toxic forms of α-synuclein shows promise with its two strategies, active and passive immunization therapies, but a direct comparative analysis of their mechanisms, efficacy, and translational potential remains limited, especially when it comes to long-term outcomes and patient-specific applicability.

In this study, passive immunization with ABBV-0805 and active immunization with UB-312 are contrasted through a literature review. This literature review compares and examines methods and results of preclinical and clinical trials of active immunization (UB-312) and passive immunization (ABBV-0805). In addition, evaluating them in terms of efficacy, safety, manufacturing complexity, and cost-effectiveness.

In preclinical models, UB-312 enhanced motor function without inducing inflammation and decreased oligomeric α-synuclein in important brain regions such as the substantia nigra and striatum. In transgenic mice, ABBV-0805 decreased phosphorylated α-synuclein, decreased soluble and insoluble aggregates, prevented the spread of pathology, and increased survival. In ex vivo human Parkinson's disease brain tissue, ABBV-0805 demonstrated selective target engagement, while early clinical studies provided preliminary pharmacokinetic and safety data. For UB-312, it produced potent, dose-dependent antibody responses with good safety. ABBV-0805 allows controlled administration of preformed antibodies, whereas UB-312 is designed to generate a sustained endogenous antibody response; whether these differences provide distinct clinical advantages remains uncertain. Both approaches demonstrated encouraging biological activity and preliminary safety profiles, supporting continued clinical investigation and the need for further validation of their therapeutic potential.

INTRODUCTION

Parkinson's disease is the second most prevalent neurodegenerative disorder after Alzheimer's disease [1][2]. Parkinson's Disease is a condition where a part of the brain degenerates, leading to severe motor and non-motor symptoms [2]. A small, dark-tinged portion of the brain, called the substantia nigra is involved in Parkinson's disease [3]. Substantia nigra is responsible for most of the brain's dopamine production [4]. Dopamine is a chemical messenger involved in many functions such as muscle control (movement), the brain's pleasure, and reward center [5]. As aging occurs, it is typical to lose cells in the substantia nigra in very slow rate, but in people with Parkinson's disease, it happens rapidly [3].

Parkinson's disease Causes

Parkinson's disease causes have yet to be identified [3], but the current research indicates that it may be a combination of genetic, environmental, and lifestyle factors [3][6][7][8]. The table number 1 summarizes the most common factors.

Table 1. Risk Factors for Parkinson's Disease [3][6][7][8][11]

Factor	Description
Age	The average of age of patients is 60 years old, and risk increases with age
Gender	Men are more likely to develop the disease than women
Genetics	10%-20% of cases are related to genetic factors related to $\alpha - synuclein$, parkin, and LRRK2
Environmental Factors	Toxin exposure, like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), head trauma, and pesticides, can increase the risk of disease development

Current research studies the brains of patients with Parkinson's disease to measure molecular changes and better understand the disease. The hallmark in the brain of a Parkinson's disease patient is the clumps of α -synuclein, Lewy bodies [3][9][10]. These bodies are associated with the degeneration of neurons [9][10]. Figure 1 summarizes the molecular mechanisms and changes found in the brain of a Parkinson's disease patient.

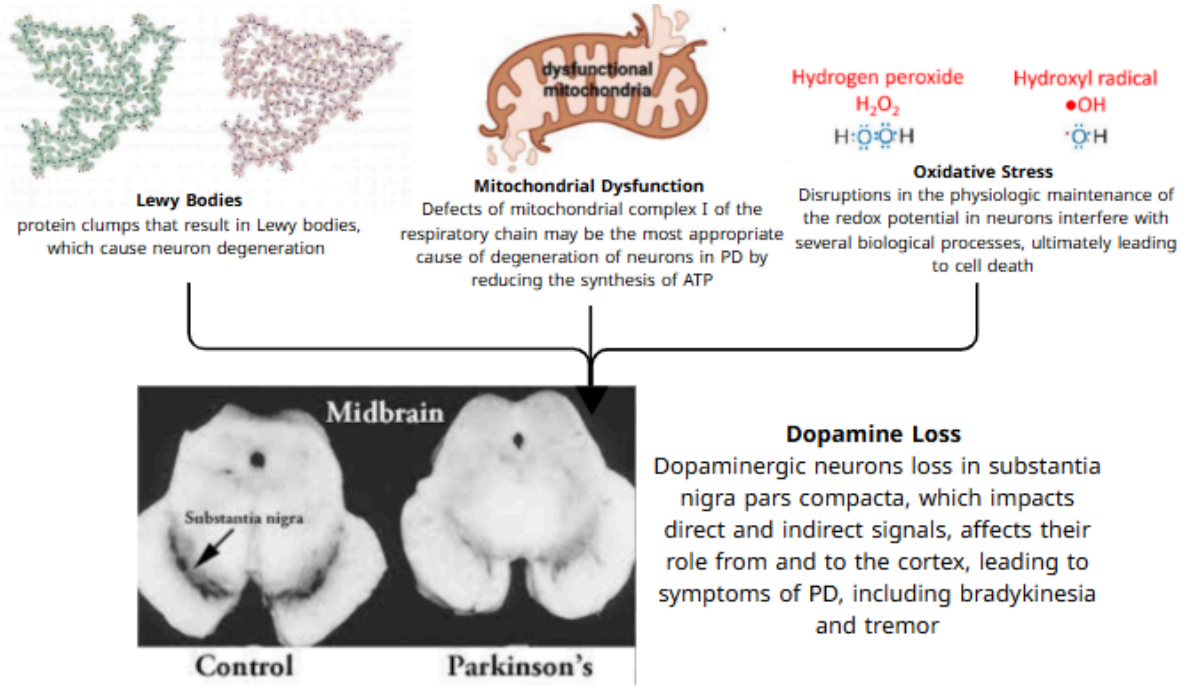


Figure 1. Molecular Mechanisms in Parkinson's Disease. Created by the author based on [6][8][9][10]

Parkinson's disease Symptoms

Parkinson's disease is recognized by its effect on movement through motor symptoms [13]. A tremor at rest is the common first-noticeable sign in Parkinson's disease patients [6]. Over time, daily functions such as walking and getting dressed can be difficult because of bradykinesia [6]. In addition to motion limitation because of muscle stiffness, which often causes severe pain [7]. Non-motor symptoms that might appear years before the motor ones [12][13]. Utilizing these early non-motor symptoms is not accurate, because they might be only biomarkers of aging, not for Parkinson's disease [6]. The table number 2 illustrates most of the motor and non-motor symptoms of Parkinson's disease.

Table 2. Motor and Non-Motor Symptoms [6][7][12][13]

Motor Symptoms	Non-Motor Symptoms
Tremor	Depression
Bradykinesia A Slowed Movement	**Anosmia** Sense of Smell Loss
Rigidity	Anxiety
Loss Of Automatic Movements	Cognitive Issues
Poor Posture and Balance	Fatigue
Speech Changes	Cognitive Issues
Writing Changes	Autonomic Nervous System Symptoms

Less Blinking	
Drooling Facial Muscle Control Loss	
Hypomimia Limited Facial Expressions	
Dysphagia Trouble Swallowing	

Parkinson's disease Standard Treatment and Current Research Direction

For motor symptoms improvements like bradykinesia, Levodopa is the standard treatment for its strong effect [18]. Its mechanism of work involves blood-brain barrier crossing, then it converts into dopamine, especially in the case of combination with carbidopa to reduce peripheral side effects and enhance brain delivery [18]. Unfortunately, the long-term utilization of Levodopa is associated with motor function complications, for example, dyskinesias [14][15].

Another treatment is dopamine agonists , which do not require conversion in the brain, it mimics dopamine by directly stimulating its receptors [16][17]. Dopamine agonists is used in the early stage of Parkinson's disease to delay the need for Levodopa [14][15]. Dopamine agonists are characterized by longer half-lives and are less affected by dietary proteins. This gives dopamine agonists a pharmacologically advantageous [14]. Through clinical trials, therapy that initiates with dopamine agonists can significantly lower the risk of developing dyskinesias compared to initiating with levodopa [15].

Current research aims to get rid of the root cause of the degradation that happens to neurons, which is the misfolded $\alpha - synuclein$ protein [19]. Current research involves the utilization of passive immunization (injection of preformed antibodies into Parkinson's disease patients) or active immunization (Vaccination) as a treatment for Parkinson's disease [20]. Through the following paragraphs, there will be an overview of $\alpha - synuclein$ before we move to passive and active immunization.

$\alpha - synuclein$ Pathogenesis in Parkinson's disease

Multiple lines of evidence highlight that $\alpha - synuclein$ has a crucial role in Parkinson's disease. Toxic $\alpha - synuclein$ forms are the primary component of Lewy Bodies and Lewy Neurites [22][23][25]. A53T is a missense point mutation, which means that one amino acid is altered: the 53rd amino acid is changed from alanine to threonine. This mutation is a result of guanine being changed to adenine at position 209 of the SNCA gene (G209A) [21][22][24].

$\alpha - synuclein$ protein is a 140-amino-acid protein involved in synaptic activity, see Figure 2. It consists of three domains:

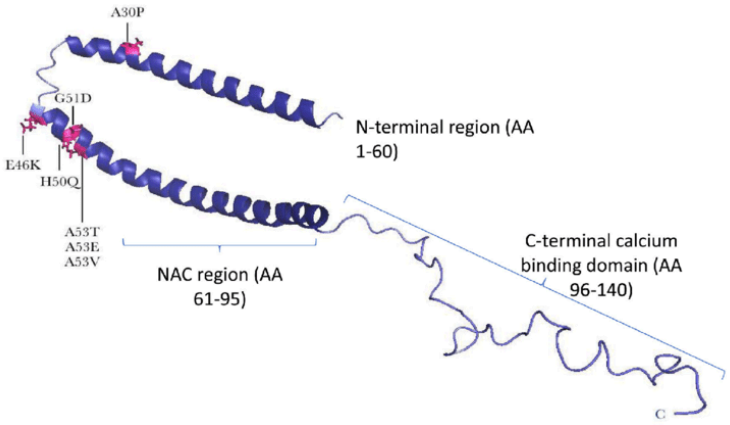
I. **N-terminal domain** – Binds lipids and contains KTKEGV repeat motifs, resembling

apolipoproteins [23][25].

II. **Non-amyloid component (NAC) domain** – A highly hydrophobic segment (residues 61–95) that promotes $\beta - sheet$ formation and aggregation [23][25].

III. **C-terminal domain** – An acidic, largely unstructured region subject to post-translational modifications, such as phosphorylation [23].

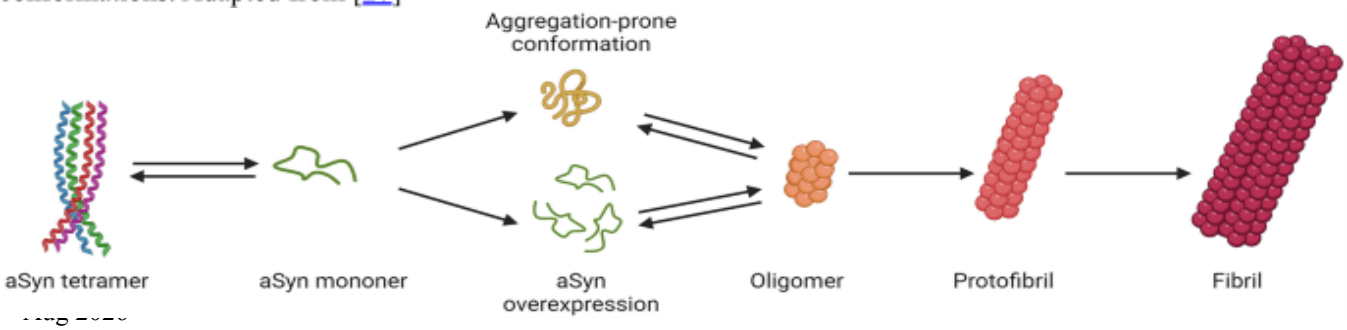
Figure 2. Structural features of the alpha-synuclein monomer. Adapted from [26]



KTKEGV repeat motifs are key mediators of normal $\alpha - synuclein$ tetramerization: Their mutation causes neurotoxicity [23][25]. Under pathological conditions, α-syn undergoes misfolding and aggregation, leading to the formation of toxic oligomers and fibrils, as illustrated in Figure 3. The NAC domain (residues 61–95) is particularly important in this transition, as it drives β-sheet formation and promotes aggregation into Lewy bodies [22][23]. Additionally, post-translational modifications (PTMs), such as phosphorylation at Ser129 (pS129), are rare in healthy brains (~4%) but become highly prevalent (~90%) in Parkinson's disease [22][23]. $\alpha - synuclein$ Protein is normally present in a monomeric, unfolded state, but can be aggregated into toxic oligomers and fibrils.

pS129 is strongly associated with aggregation. Studies indicate that $\alpha - synuclein$ toxicity arises from oligomeric and fibrillar forms rather than monomers. Overexpression or triplication of SNCA can drive aggregation, and misfolded $\alpha - synuclein$ may propagate between neurons in a prion-like manner, spreading pathology throughout the brain [22][23].

Figure 3. Monomeric is an intrinsically disordered protein that constantly undergoes transformation into different conformations. Adapted from [27]



Current Research in Parkinson's Disease Treatment and the Objective of this Study

The latest research introduces a new approach, which is immunization therapy that targets toxic forms of $\alpha - synuclein$ protein [28]. Although it faces challenges like optimizing biomarkers, dosage, and patient selection, it holds promise in eliminating $\alpha - synuclein$ aggregates, halting the progression, and improving motor symptoms [29]. This approach, combining active and passive immunization therapy, has promising potential for the treatment of Parkinson's disease and other synucleinopathies [28].

In this comparative study, the following research question will be discussed: Which immunotherapy approach—active or passive—holds the greatest promise for the treatment of Parkinson's disease and other synucleinopathies, when evaluated in terms of efficacy, safety, manufacturing complexity, and cost-effectiveness?

Active immunization therapy is the process by which the patient's immune system is triggered to stimulate an immune response when the patient is injected with a vaccine [30]. In the context of Parkinson's disease, a vaccine is designed to elicit an immune response against toxic forms of $\alpha - synuclein$ [30]. UB-312 vaccine generates antibodies targeting harmful $\alpha - synuclein$ aggregates and its Phase 1 clinical trial demonstrated that UB-312 was well-tolerated and reduced $\alpha - synuclein$ clumps [31].

Passive immunization therapy is the process by which pre-formed antibodies are introduced to the patient to neutralize specific targets, specifically monoclonal antibodies like ABBV-0805, which are being explored as a potential for Parkinson's disease therapy [32]. ABBV-0805 antibodies selectively target soluble oligomeric and fibrillar $\alpha - synuclein$, specifically at the C-terminal region (amino acids 121–127) [33]. In Parkinson's disease mouse models, ABBV-0805 significantly reduced pathological $\alpha - synuclein$ aggregates, extended survival, and lowered CSF phosphorylated $\alpha - synuclein$ levels [34], and in MSA (multiple system atrophy) animal models, treatment led to reduced neuroinflammation and decreased $\alpha - synuclein$ inclusion burden [35].

METHODS

A structured literature review was conducted to compare active (UB-312 vaccine) and passive (ABBV-0805 antibody) immunization therapies targeting toxic forms of α-synuclein in Parkinson's disease. Relevant peer-reviewed preclinical and clinical studies were identified through searches in databases including PubMed, Scopus, and Google Scholar using combinations of keywords such as "α-synuclein", "Parkinson's disease", "UB-312", "ABBV-0805", "active immunization", and "passive immunization". Studies were selected based on relevance to immunotherapy, inclusion of experimental data, and availability of detailed outcomes related to efficacy, safety, or pharmacokinetics. Both animal

and human studies were included, though available clinical data for ABBV-0805 were limited. Selected articles were reviewed to extract outcomes on four parameters: efficacy, safety, manufacturing complexity, and cost-effectiveness.

UB-312 Vaccine Preclinical Trial Methods

In study [36], the preclinical evaluation of UB-312 employed a transgenic mouse model designed to replicate key features of early Parkinson's disease pathology. Thy1SNCA/15, which is a transgenic mouse model, was in use. The special thing about this model is that it overexpresses human wild-type $\alpha - synuclein$ protein under the Thy1 promoter control. In addition, it stimulates early $\alpha - synuclein$ pathology without aggregates of Lewy Bodies. The mice utilized through this study were Thy1SNCA/15 ones and wild-type ones, which were bred and housed under standard conditions. The conditions involve a 12-hour light/dark cycle and free food and water access.

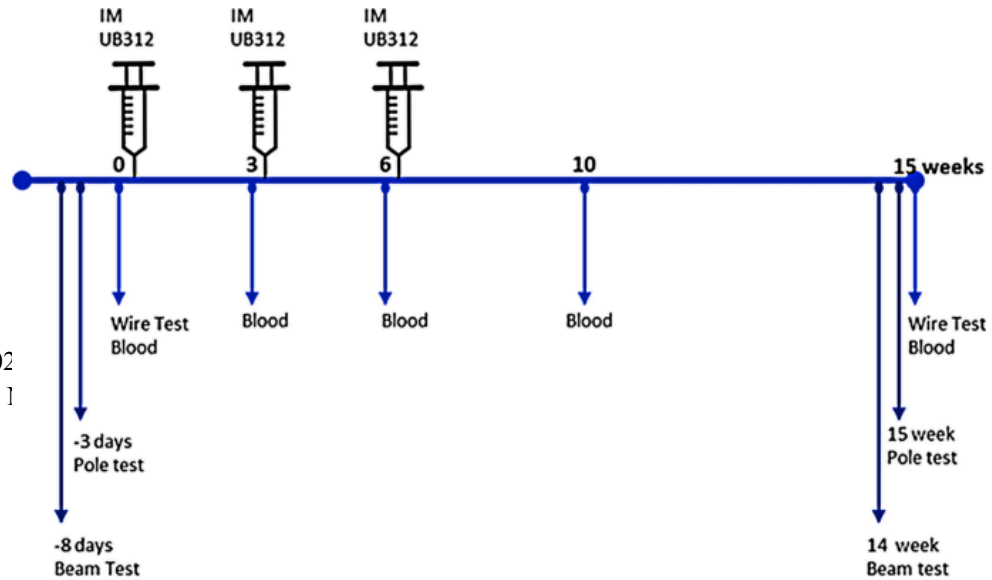
Immunization Protocol

To assess the immunogenicity and effects of UB-312, at the age of the tenth week, intramuscular injection for a total of three doses every three weeks was determined for mice. The whole immunization protocol is shown in Figure 4. The therapy groups are:

- **UB-312 Group**: Thy1SNCA/15 mice (n = 29) received 40 µg UB-312 per injection.
- **Adjuvant Control Group**: Thy1SNCA/15 mice (n = 27) and WT littermates (n = 22) received adjuvant only (Adju-Phos® and CpG1).

The structure and manufacturing process of the UB-312 vaccine were as follows, $\alpha - synuclein$ peptide conjugated to UBITh® T-helper peptides, then it was mixed with adjuvants for B-cell response stimulation while avoiding autoreactive T-cell activation. It is necessary to highlight that blood was collected before each injection and again at weeks 10 and 15 post-prime to assess $anti - \alpha - synuclein$ antibody titers utilizing an enzyme immunoassay (EIA) kit targeting the α-Syn region K97–D135.

Figure 4. Schematic timeline of the immunization and behavioral testing schedule for UB-312-treated and control mice. Adapted from [37]



Behavioral Testing

They were conducted to evaluate the functional impact of immunization. There were behavioral assessments for mice at different times, the first time before the start of immunization and at the fifteenth week. These tests have been conducted on separate days, with appropriate habituation, and in specific order. The order was as follows:

- **Challenging Beam Test**: This test was utilized to evaluate balance and coordination. The rats were required to traverse a one-meter-long beam with progressively narrower sections, and five trials were conducted daily for three days. After this training, performance was tested on a wire-covered beam to assess foot-sliding errors.
- **Pole Test**: This test was utilized to evaluate motor planning and control. Rats were placed on a vertical pole and were subjected to an 180-degree rotation and then a landing. Each rat underwent three days of habituation, with up to five trials per session, followed by one test.
- **Wire Hanging Test**: This test was utilized to test grip strength and endurance. This test was assessed on mice two times, once before and once after immunization. They were placed hanging upside-down on a rotating wire loop. Time to fall was recorded, with a maximum cut-off of 5 minutes. There were excluded trials that involved improper behavior, such as jumping.

All behavioral tests were conducted by an investigator blinded to treatment allocation.

Tissue Collection and Preparation

Post-mortem analyses were performed to examine molecular and histological outcomes. After the end of the fifteenth week, mice were deeply anesthetized and given a solution for either immunological or biochemical analysis. The tissue collection process for histological and biochemical analysis was as follows:

- **Immunohistochemistry:** Mice were perfused with Phosphate-Buffered Saline followed by 4% paraformaldehyde. Brains and gut tissues, specifically the parts, duodenum and proximal colon, were dissected, post-fixed in paraformaldehyde, then cryoprotected in 30% sucrose.
- **Biochemical analysis**: Mice were perfused with ice-cold PBS. Brain regions, specifically the cortex, hippocampus, and striatum, were dissected and snap-frozen for protein analysis.

Immunohistochemistry

Sections of the gut and sagittal brain (20 μm) were prepared. Following an overnight incubation with primary antibodies (including MJFR1 for $\alpha - synuclein$) and secondary fluorescent antibodies, sections

were blocked in goat serum. GFAP (astrocytes), Iba1 (microglia), CD3 (T-cells), and ICAM1 (endothelial activation) were among the glial and inflammatory markers that were employed. When necessary, fluorescence imaging techniques or DAB were used.

Western Blot

To quantify protein expression, Western blotting was performed using RIPA-buffer homogenates of cortex, hippocampus, and striatum. Utilizing Radioimmunoprecipitation Assay buffer (RIPA buffer) with inhibitors, brain tissues were homogenized. Protein concentrations were determined using the Bovine Serum Albumin assay (BSA assay). For the separation of oligomeric and monomeric $\alpha - synuclein$ species, Native PolyAcrylamide Gel Electrophoresis (PAGE) was used. Proteins were transferred to nitrocellulose membranes and probed with MJFR1 antibody. Revert 700 total protein stain was used for normalization.

Data Analysis

The study involved immunoblots, fluorescence microscopy, and DAB immunostained tissue sections. Immunoreactive $\alpha - synuclein$ bands were normalized for SDS-PAGE and native PAGE. The percentage area of immunoreactivity was calculated using FIJI software, and statistical analysis was conducted using GraphPad Prism software. Two-way ANOVA was used for behavioral analysis, and T-tests for $\alpha - synuclein$ immunoreactivity, and one-way ANOVA for inflammatory markers. Differences were considered significant when $p < 0.05$.

UB-312 Vaccine Clinical Trial Phase 1 Methods

The goal of this clinical trial [38] is the evaluation of the safety, tolerability, and immunogenicity of the UB-312 vaccine in healthy adult volunteers. As a result, a randomized, placebo-controlled, dose-escalation phase 1 trial was conducted. The study design and execution were conducted in the Netherlands, involving 50 volunteers divided into 8 groups, with follow-up extending to 44 weeks after the first dose.

Participants

Volunteers were recruited and stratified into 7 groups, each group consisting of 6 individuals, except one group, the placebo group, which consisted of 8 individuals, and they received 3 matched injections. Each group received one of the following regimens which is illustrated in Table 3:

Table 3. Dosing Regimens Used in the UB-312 Phase 1 Clinical Trial

Aspect	First Dose (in μg)	Second Dose (in μg)	Third Dose (in μg)
First Group	40	40	40
Second Group	100	100	100
Third Group	300	300	300
Fourth Group	1000	1000	1000

Fifth Group	2000	2000	2000
Sixth Group	40	300	300
Seventh Group	40	1000	1000

Immunization Schedule

Participants received three intramuscular (IM) injections; 7 groups received intramuscular injections of UB-312 vaccine, and the eighth group received intramuscular injections of placebo, according to the following schedule to allow immune priming and boosting:

- Week 1
- Week 5
- Week 13

Sample Collection and Monitoring

The blood sample collection happened according to the following schedule:

- At baseline
- 1 week after each injection
- Every 4 weeks up to week 21

The Cerebrospinal fluid (CSF) collection happened according to the following schedule:

- At baseline
- At week 21

Samples were assessed as:

- $Anti-\alpha-synuclein$ antibodies, which target the K97–135 C-terminal region, in blood and CSF
- Total and free $\alpha-synuclein$
- Misfolded $\alpha-synuclein$ oligomers using Protein Misfolding Cyclic Amplification (PMCA)

Participants' Safety Assessments

For volunteers' safety, they were monitored for any adverse events throughout the whole process of the study. Additionally, the assessment was extended to an additional 23 weeks. Expected adverse events such as local reactions, systemic symptoms, and serious adverse events. Local reactions, such as pain and redness, and systemic symptoms, such as headache, cold-like symptoms, and flu-like symptoms.

Data Analysis

Over time, antibody titers were measured and examined. Blood-brain barrier penetration was estimated using serum-to-CSF ratios, which were compared between dosage groups. Confidence intervals and descriptive statistics were presented. Since the study was exploratory and mainly concentrated on safety and immunogenicity, no formal hypothesis testing was done at this time.

ABBV-0805 ANTIBODIES PRECLINICAL TRIAL METHODS

In study [39], two transgenic mouse models of Parkinson's disease were used, the first one is (Thy-1)-h[A30P] $\alpha - synuclein$ transgenic mice, and the second one is A53 T+/− (M83) mice. These models exhibit progressive motor deficits progression and $\alpha - synuclein$ pathology. All experiments were approved by ethical committees and conducted by EU animal welfare guidelines.

Treatment Protocols and PFF Inoculation

Depending on the study, mice were given intraperitoneal (i.p.) injections of mAb47, the murine form of ABBV-0805, at doses varying from 0.25 to 50 mg/kg. Preformed fibrils (PFFs) of $\alpha - synuclein$ were injected into the brain or muscle of mice in certain experiments to hasten pathology.

- **Prophylactic studies:** Treatment began before Preformed fibrils injection.
- **Therapeutic studies:** Treatment began after Preformed fibrils injection.
- **Survival studies:** Older mice (12 months) were treated biweekly with 10 mg/kg mAb47 until the onset of severe motor symptoms.

Sonicated $\alpha - synuclein$ Preformed fibrils were injected intramuscularly into the gastrocnemius muscle in pertinent studies. In A53T+/-mice, stereotaxically into the anterior olfactory nucleus.

Tissue Collection and Processing

Mice were put down at the end of the study (when symptoms appeared or after predetermined amounts of time). The spinal cord and brain were gathered. The tissues were:

- homogenized and extracted with formic acid for insoluble aggregates and TBS/Triton for soluble fractions.
- processed for biochemical tests, such as Western blot and ELISA, or fixed for immunohistochemistry.

Immunohistochemistry and Quantification

Sections of the brain and spinal cord were stained with pSer129 antibodies to identify phosphorylated, pathological $\alpha - synuclein$ and with LB509 to identify the total human $\alpha - synuclein$. Antigen retrieval, blocking, and secondary antibody incubation were all done according to standard procedures. Depending on the labeling method, either fluorescence or brightfield microscopy was used for detection.

Immunoreactive area, density, and inclusion count were measured using image analysis software with an emphasis on areas like the hippocampus and midbrain. To assess the impact of the antibody on $\alpha - synuclein$ pathology, analyses were performed blind to treatment and compared between treatment and control groups.

Biochemical Assays

Both soluble and insoluble fractions of brain tissue were examined to assess $\alpha - synuclein$ pathology at the biochemical level. Following protein extraction with detergents and formic acid, the proteins underwent MSD (Meso Scale Discovery) electrochemiluminescence assays, which allow for the

quantitative and highly sensitive detection of both total and phosphorylated $\alpha - synuclein$. Levels from various treatment groups and time points were compared using these assays.

Thioflavin-T fluorescence assays, which specifically identify $\beta - sheet - rich$ Fibrillar structures characteristic of $\alpha - synuclein$ aggregation, were used to further evaluate protein aggregation. Additionally, dot blot and Western blot analyses were performed to differentiate between the various conformational states of $\alpha - synuclein$, such as monomers, oligomers, and high-molecular-weight aggregates. Together, these techniques provided a comprehensive biochemical evaluation of ABBV-0805's therapeutic effect.

Pharmacokinetics

After a single intravenous dose, the pharmacokinetic profiles of mAb47 were evaluated in wild-type mice. Key parameters like half-life, C_{max}, and brain:plasma ratios were computed using standard analysis software, and plasma and brain concentrations were monitored over time.

ABBV-0805 ANTIBODIES CLINICAL TRIAL PHASE 1 METHODS

The safety, tolerability, pharmacokinetics (PK), and immunogenicity of ABBV-0805 in healthy adult volunteers were assessed in a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study [40]. The study was conducted at a single clinical site and was first-in-human (FIH).

44 participants in all, ranging in age range from 30 to 65, were enrolled in five dose cohorts. Eight participants made up each cohort; two received a placebo and six received a single intravenous (IV) infusion of ABBV-0805. Each participant received a single dose, and dose levels rose across cohorts. The subjects were blinded to their treatment allocation and assigned at random.

Assessments and Sample Collection

In this study, safety evaluations were carried out to guarantee participant's health and identify any health risks. Regular vital sign monitoring (blood pressure, heart rate, respiratory rate, and temperature), electrocardiograms (ECGs) to assess cardiac function, and a full battery of laboratory tests, including hematology and clinical chemistry, were all part of these evaluations. To identify any immediate or delayed effects, participants were closely monitored at predetermined intervals before and following drug administration, and adverse events were continuously recorded.

Serial blood samples taken at various intervals following ABBV-0805 infusion were used for PK analysis. To compute pharmacokinetic parameters like maximum concentration (C_{max}), time to reach peak

concentration (T_{max}), half-life ($t½$), and clearance rate, as well as serum drug concentrations over time, these samples were analyzed. This made it easier to describe how the drug behaved in the human body. Anti-drug antibodies (ADAs) were also assessed to track immunogenicity, which may affect the safety or efficacy of the medication.

At different stages of the study, biomarker samples were taken from participants in addition to safety and PK sampling. The purpose of these samples was exploratory analysis to look into possible biological effects of ABBV-0805, such as how it might affect $\alpha - synuclein$ levels or associated pathological pathways. Although the biomarkers measured were not mentioned in the abstract, such information would normally offer a preliminary understanding of target engagement and mechanistic effects in advance of Parkinson's disease clinical development.

RESULTS

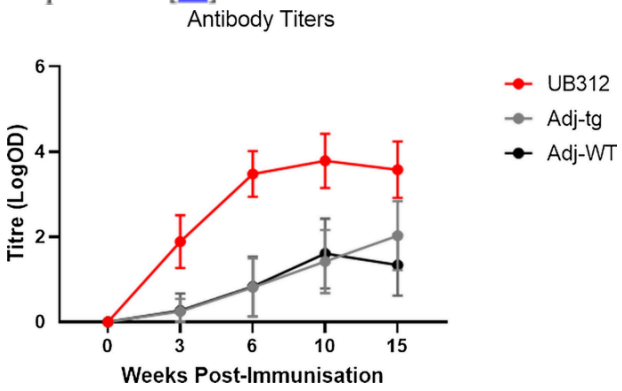
Studies were included in the review, comprising both preclinical and early-phase clinical trials. The results are organized according to the four comparison criteria: efficacy, safety, manufacturing complexity, and cost-effectiveness. Within each criterion, findings related to UB-312 and ABBV-0805 are summarized, drawing on experimental outcomes from animal models and available clinical trial data in humans.

UB-312 Vaccine Preclinical Trial Results [36]

Antibody Titres

The Thy1SNCA/15 mice that received UB-312 vaccine immunization induced strong humoral responses. By the first 6 weeks, $Anti - \alpha - synuclein$ antibody titers, which target the K97–D135 region, increased rapidly, with a peak between weeks 6 and 10, and remained stable by week 15, which is illustrated in Figure 5. The minimal background responses shown by the adjuvant-only groups were 2-3 orders of magnitude lower than those of the UB-312 vaccine group.

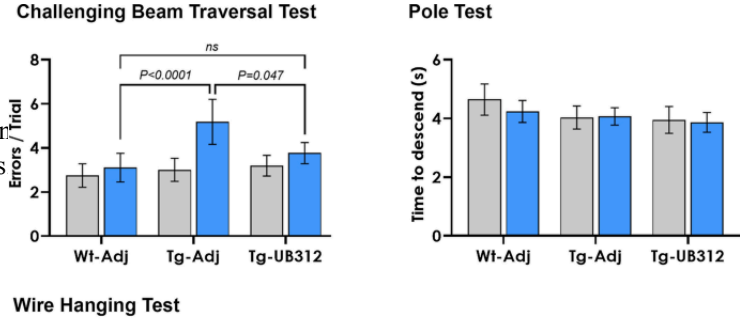
Figure 5. UB-312 induced high anti-α-synuclein antibody titres in Thy1SNCA/15 mice, sustained through week 15. Adapted from [41]



Motor Performance

In transgenic mice, UB-312 significantly maintained motor function 15 weeks after treatment. UB-312-treated mice preformed similarly to wild-type mice in the difficult beam test and made fewer foot slips than adjuvant controls ($p < 0.0001$). Compared to adjuvant-treated controls, treated mice displayed

Figure 6. UB-312-treated mice showed improved performance in the beam and wire tests compared to controls. No difference was seen in the pole test. Adapted from [42]



noticeably longer hang times (p = 0.0095) in the wire hanging test, which is illustrated in Figure 6. The pole test revealed no discernible variations between the groups.

Reduction of Brain α-Synuclein Oligomers

A significant reduction in oligomeric $\alpha - synuclein$ is shown by Western blot analysis, but the same was not shown for the monomeric forms of $\alpha - synuclein$. The brain regions of mice that received the UB-312 vaccine compared to controls, as follows:

- Hippocampus: ↓27.8% (p = 0.049)
- Striatum: ↓27.9% (p = 0.045)
- Cortex: ↓49.8% (p = 0.035)

Neuroinflammation and Glial Activation

GFAP (Astrocytes) immunoreactivity was similar in all groups [44] (Press the in-text citation to reach the figure), indicating that UB-312 did not affect astrocyte activation. Except a slight increase in the substantia nigra, microglial activation, as measured by Iba1(Microglia), remained constant in most brain regions [45]. Mice treated with UB-312 showed markedly increased CD64 (FcγRI) immunoreactivity in the substantia nigra, striatum, hippocampus, and cortex, indicating increased Fc-mediated phagocytic activity [46]. There was no relationship between antibody titres and CD64 levels.

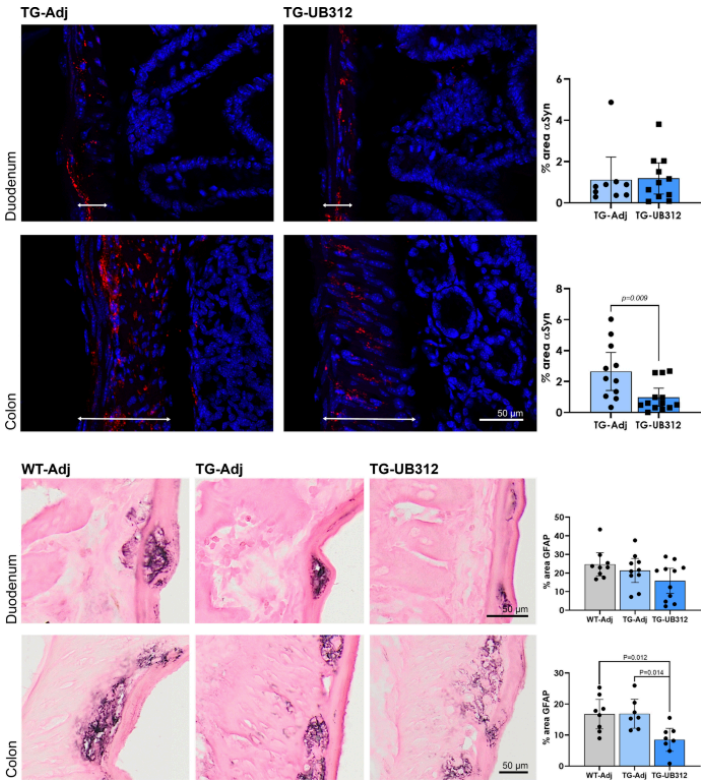
T Cell Infiltration and Endothelial Activation

There was no T-cell infiltration found in any group's brain tissue, and there was no difference in ICAM1 expression on cerebral endothelial cells between the UB-312 and control groups, suggesting no pro-inflammatory immune activation [47].

Colon α-Synuclein Pathology and Enteric Glial Activation

Immunization with UB-312 significantly decreased the accumulation of $\alpha - synuclein$ in the colon (∓63%, p = 0.0093), but not in the duodenum, which is illustrated in Figure 7. Additionally, GFAP-positive glial cell reactivity was significantly decreased (↓50%, p = 0.014) in the colonic myenteric ganglia, suggesting a possible therapeutic effect on gastrointestinal α-synuclein pathology.

Figure 7. UB-312 reduced α-synuclein and glial activation in the colon but not the duodenum. Adapted from [48]

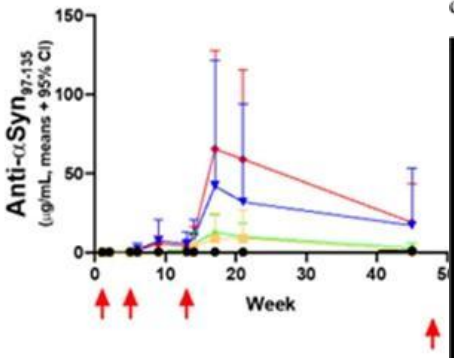


UB-312 Vaccine Clinical Trial Phase 1 Results [38]

Antibody Response

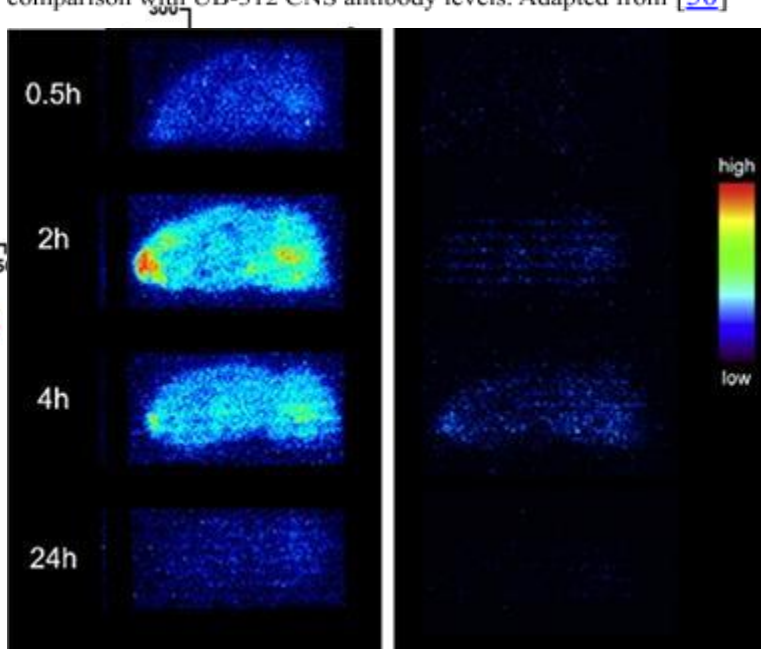
In healthy adults, UB-312 produced a potent, dose-dependent antibody response. Blood levels of anti-C-terminal α-synuclein antibodies were considerably higher in participants who received three doses of 300 µg or 100 µg. Lower doses and placebo groups exhibited negligible responses, whereas the 300 µg group had the highest titres, peaking around week 21, which is illustrated in Figure 8.

Figure 8. Antibody levels in blood (left) and CSF (right) after 3 doses of UB-312. Highest titres seen with 300 µg (red), followed by 100 µg (blue). Minimal response in lower-dose and plac



Antibody levels in the cerebrospinal fluid showed a similar trend, with the 300 µg group exhibiting the highest concentrations. About 0.2% of serum levels of antibodies were found in cerebrospinal fluid, indicating partial blood–brain barrier penetration, which is illustrated in Figure 9.

Figure 9. PET scans showing improved brain uptake of SynO2-TfR (left) vs. SynO2 (right) via transferrin receptor targeting. Used for comparison with UB-312 CNS antibody levels. Adapted from [50]



Safety and Tolerability

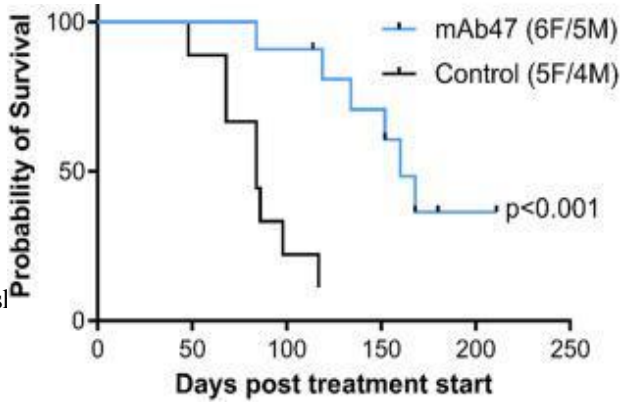
Well-tolerated doses up to 300 µg were found. Headache, cold-like symptoms, and injection site discomfort were examples of mild adverse events. Dose escalation was stopped because one participant experienced a mild flu-like reaction to the 1000 µg dose. There were no significant adverse events noted.

ABBV-0805 Antibodies Preclinical Trial Results [39]

Survival and Motor Function Improvement in A30P Mouse Model

To assess its impact on disease progression and lifespan, mAb47 was given to the aggressive (Thy-1)-h[A30P] mouse. Animals were given an intraperitoneal injection of 10 mg/kg mAb47 every two weeks starting at 12 months of age. Treatment continued until the animals achieved a humane endpoint associated with motor

Figure 10. mAb47 treatment significantly prolongs survival in A30P mice. Adapted from [51]

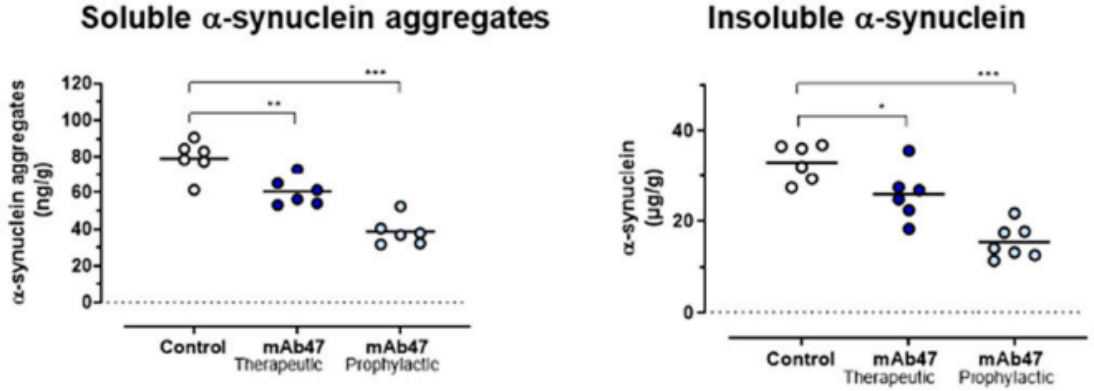


decline. Mice treated with mAb47 exhibited a remarkable increase in median survival to 160 days, compared to vehicle-treated controls with 84 days, which is illustrated in Figure 10. This improvement provides preclinical support for the potential disease-modifying activity of ABBV-0805, although whether these effects translate into slowed neurodegeneration or delayed disease progression in humans requires further validation.

Impact on $\alpha - synuclein$ Pathology with Prophylactic and Therapeutic Regimens

A study on early-stage Parkinson's disease used a PFF-seeded (Preformed fibrils) version of the A30P model to test mAb47's ability to alter $\alpha - synuclein$ pathology. Both prophylactic and therapeutic treatment paradigms were used, with mAb47 administered every two weeks. The prophylactic group had lower levels of soluble and insoluble $\alpha - synuclein$, suggesting early intervention could prevent pathological development, which is shown in Figure 11. The treatment group saw a significant reduction in soluble and insoluble $\alpha - synuclein$ accumulation, indicating the potential for early intervention.

Figure 11. Soluble and insoluble α-synuclein reduction following mAb47 treatment. Adapted from [52]



Reduction in Phosphorylated $\alpha - synuclein$

Neurotoxicity in Parkinson's disease is closely associated with phosphorylated $\alpha - synuclein$ at serine 129 (pSer129). Prophylactic mAb47 treatment significantly decreased pSer129 levels from 43 µg/g to just 2.3 µg/g, indicating a ~95% reduction, according to brain homogenates. Early immunotherapy may be able to stop important stages of aggregate formation, as evidenced by the almost total suppression of pathological $\alpha - synuclein$ phosphorylation.

Brain pSer129 decreased by 38% in the treatment group, from 43 µg/g to 27 µg/g. Additionally, cerebrospinal fluid pSer129 levels significantly decreased in both treated groups, mirroring brain findings, as illustrated in Figure 12. These reductions in central and peripheral biomarkers suggest that ABBV-0805 may have pharmacodynamic activity against pathological $\alpha - synuclein$, although the clinical significance of these biomarker changes requires further validation.

Figure 12. Significant reduction of pSer129 α-synuclein in brain and CSF. Adapted from [52]

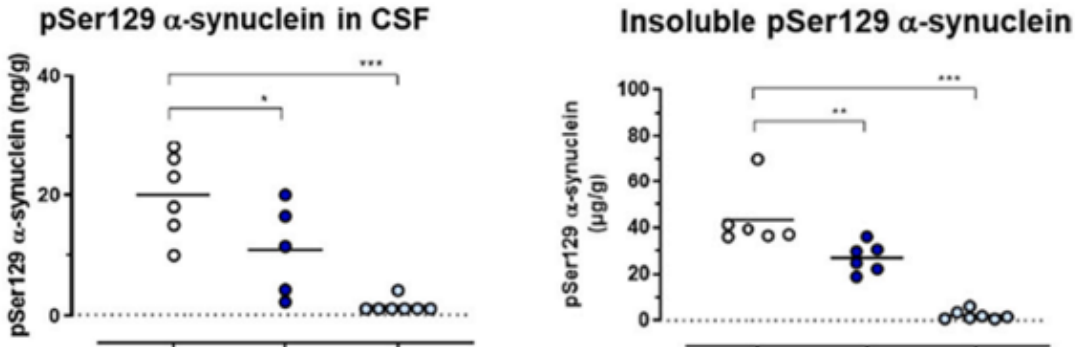
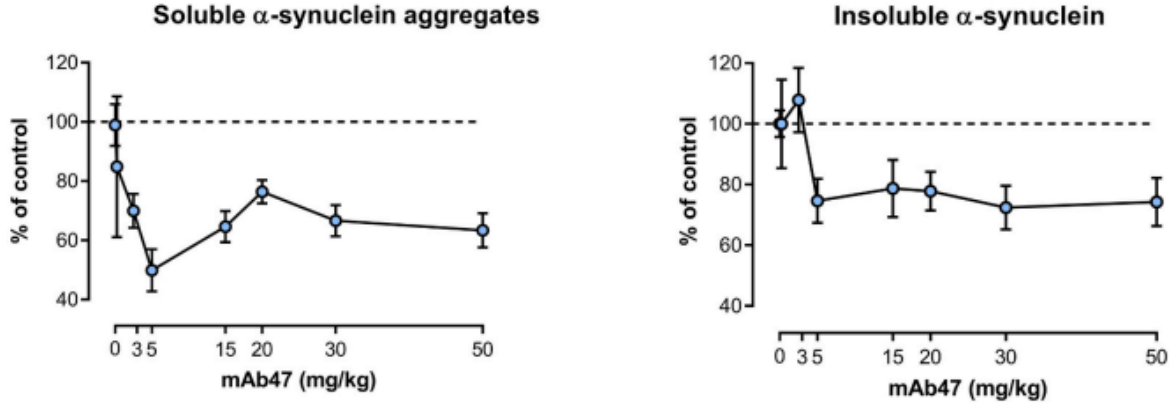


Figure 14. pSer129 α-synuclein staining in the contralateral side of hippocampus in vehicle-treated (A) and mAb47-treated (20 mg/kg), i.p. (B) A53T+/− mice following intra-AON PFF injection. (C). Mean p129 α-synuclein staining density (±SEM) in the pyramidal layer of the contralateral CA1 is shown for vehicle and mAb47. *p < 0.05 vs control; unpaired t-test. Adapted from [54]

Dose-Dependent Efficacy in Reducing Pathology

Therapeutic mAb47 was tested at doses ranging from 5 to 50 mg/kg one week after Preformed fibrils injection. Results showed a 20-50% reduction in soluble and insoluble α-synuclein aggregates at doses as low as 5 mg/kg. No increase in reductions was observed when doses increased above 5 mg/kg, suggesting a plateau effect in target engagement or clearance capacity, which is illustrated in Figure 13. This finding is crucial for dosing strategy in upcoming clinical trials and suggests 5-10 mg/kg as a reasonable initial range in human research.

Figure 13. Dose-response plateau in α-synuclein aggregate reduction at ≥5 mg/kg. Adapted from [53]



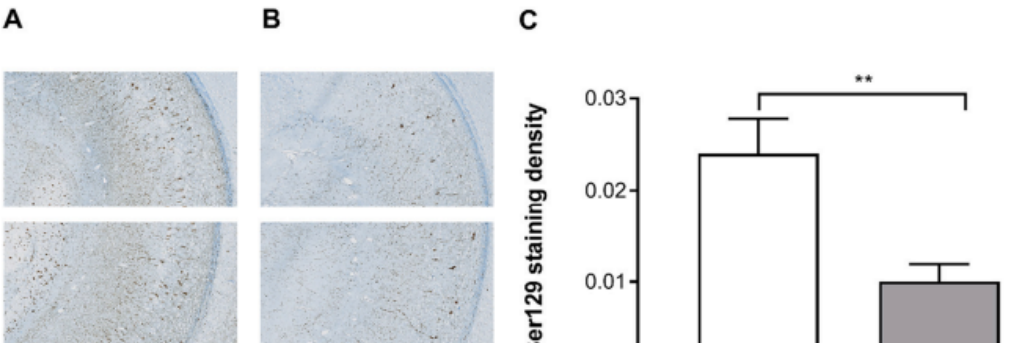
Inhibition of Pathology in A53T Model

In a different study, Preformed fibrils (PFF) were stereotactically injected into the anterior olfactory nucleus of A53T+/− transgenic mice, a model with slower pathology progression, to cause localized pathology and enable trans-synaptic propagation analysis. Mice were given weekly injections of mAb47 (20 mg/kg) for 16 weeks after the first week.

In comparison to controls, mAb47-treated mice showed a 58% decrease in phosphorylated α-synuclein pathology in the contralateral hippocampus at endpoint. This significant decrease in a distant, untreated area of the brain suggests that ABBV-0805 may reduce pathological α-synuclein spread in this model rather than acting solely on local aggregation. These findings suggest that the antibody may influence disease-associated pathology after pathology has been established, although this effect requires further validation in clinical studies.

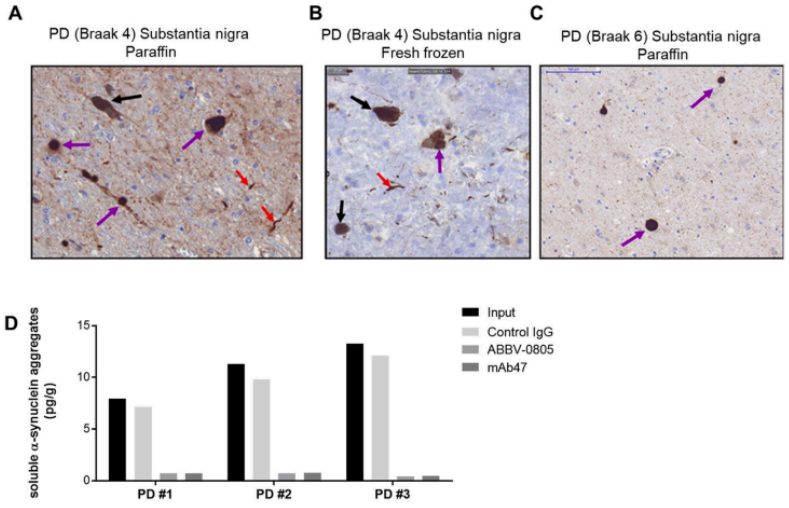
Confirmed Target Engagement in Human PD Brain

Postmortem brain sections from patients (Braak stage 4-6) were used to test ABBV-0805 antibodies for clinical relevance. The antibody's capacity to identify disease-relevant aggregates in human tissue was



validated by its selective binding of Lewy Bodies (LBs) and Lewy Neurites (LNs). Crucially, ABBV-0805 antibodies were able to immunodeplete almost all oligomeric $\alpha - synuclein$ from soluble brain homogenates, leaving only monomers. These findings support the translational relevance of the preclinical results and provide evidence of target selectivity and functional activity, as in Figure 15. Its selective binding to pathological conformers supports further investigation as a potential therapeutic candidate.

Figure 15. ABBV-0805 immunohistochemical staining pattern in substantia nigra from paraffin (A) and fresh frozen (B) sections. (C) PD cases Braak 4-6 with LB and neurites indicated. (D) Immunodepletion of oligomeric α-synuclein in PD brain homogenates using ABBV-0805 compared to control IgG and mAb7. Adapted from [55]



ABBV-0805 Antibodies Clinical Trial Phase 1 Results [40]

Single ABBV-0805 intravenous infusions administered to healthy volunteers in the first-in-human study have been well-tolerated, with no concerning safety findings related to adverse events, laboratory results, vital signs, or electrocardiograms. Preliminary data suggest a favorable Pharmacokinetics, pharmacodynamic, and immunogenicity profile for ABBV-0805.

DISCUSSION

Parkinson's disease prevails as a challenge in neurodegenerative disease medicine, which is driven by complex etiology and a dopaminergic neurons progressive degeneration in the substantia nigra brain region. The misfolded $\alpha - synuclein$ protein grows as evidence for the reason of disease pathogenesis and progression. The technology of immunotherapy in Parkinson's disease is a promising tool to get rid of $\alpha - synuclein$ toxicity by clearing or neutralizing it. Through this study, the following research question is tried: "Which immunotherapy approach—active or passive—holds the greatest promise for the

treatment of Parkinson's disease and other synucleinopathies, when evaluated in terms of efficacy, safety, manufacturing complexity, and cost-effectiveness?**"**

Active Immunization Therapy: UB-312 Vaccine

The UB-312 is designed to produce antibodies against the toxic C-terminal forms of $\alpha - synuclein$. According to the results of the preclinical trial, the levels of oligomeric $\alpha - synuclein$ in the cortex, striatum, and hippocampus of Thy1SNCA/15 mice were significant reductions. Significant enhancements in motor function were associated with this, specifically in difficult beam and wire-hanging tasks. Crucially, there was no T-cell infiltration, endothelial activation, increase in astrocyte, or microglial reactivity, suggesting that the UB-312 vaccine does not cause CNS inflammation.

In healthy adults, UB-312 triggered a strong, dose-dependent antibody response in a clinical trial [56]; the highest titres were observed at 300 µg. Antibodies were detected in cerebrospinal fluid at approximately 0.2% of serum levels. Subsequent Phase 1 clinical evaluation in patients with Parkinson's disease demonstrated that UB-312 was generally well tolerated and induced anti-α-synuclein antibodies in serum and cerebrospinal fluid. Exploratory analyses showed a significant reduction in α-synuclein seeds in cerebrospinal fluid in a subset of UB-312-treated patients; however, no statistically significant differences were observed in clinical scales. Thus, the available clinical evidence primarily supports safety, tolerability, and immunogenicity, while clinical efficacy and disease modification remain unestablished.

Passive Immunization: ABBV-0805 Antibodies

ABBV-0805 uses pre-formed antibodies to bind soluble aggregated α-synuclein. ABBV-0805 reduced soluble and insoluble $\alpha - synuclein$, reduced phosphorylated $\alpha - synuclein$ (pSer129), and stopped trans-synaptic spread of pathology in aggressive (Thy-1)-h[A30P] and A53T+/− lines mouse models. In addition, it nearly doubled median survival in the aggressive A30P model, providing a preclinical finding consistent with potential disease-modifying activity.

Phase 1 trials demonstrated that ABBV-0805 had a good pharmacokinetic and safety profile, though clinical data is still being gathered. Systemic exposure was confirmed by antibody detection without eliciting strong immune responses, and no severe side effects were reported. Strong translational potential was also indicated by ex vivo studies conducted in human Parkinson's disease brains, which verified the antibody's capacity to bind Lewy bodies and deplete toxic soluble $\alpha - synuclein$.

Biomarker and Clinical Endpoint Challenges

A further challenge is determining whether reductions in pathological α-synuclein biomarkers represent meaningful therapeutic effects. Measures such as soluble or insoluble α-synuclein, phosphorylated α-synuclein at serine 129, and α-synuclein seed amplification provide information about pathological burden or target engagement, but they have not been established as universally validated surrogate endpoints for clinical benefit in Parkinson's disease. A biomarker may change in response to treatment

without necessarily producing a corresponding improvement in motor symptoms, non-motor symptoms, or the rate of disease progression. Therefore, reductions in α-synuclein pathology observed in animal models should not by themselves be interpreted as evidence of disease modification in patients.

This distinction is particularly relevant to UB-312, for which a Phase 1 study in patients with Parkinson's disease demonstrated immunogenicity and a reduction in α-synuclein seeds in cerebrospinal fluid in a subset of participants, while exploratory clinical scales did not show statistically significant differences. This illustrates the difference between demonstrating biological target engagement and demonstrating clinical efficacy. Similarly, reductions in pSer129 and other α-synuclein measures observed with ABBV-0805 in animal models demonstrate pharmacodynamic activity within those experimental systems but do not establish that equivalent biomarker changes would slow human disease progression. Future trials should therefore evaluate biomarker changes alongside validated clinical outcomes and measures of disease progression.

Comparative Analysis

In terms of efficacy, although both treatments reduced α-synuclein burden in preclinical models, UB-312's capacity to generate endogenous antibody responses may provide sustained antibody exposure; however, whether this translates into longer-lasting clinical effects, particularly in early-stage Parkinson's disease, remains uncertain. Although passive immunization allows direct administration of preformed antibodies, whether this translates into faster or greater clinical benefit than active immunization remains uncertain.

In terms of safety, in preliminary preclinical and early-phase clinical studies, both approaches demonstrated generally acceptable tolerability. However, because active immunization induces an endogenous immune response against a self-protein target, theoretical concerns regarding unintended immune effects warrant continued monitoring. Although UB-312 studies did not observe this risk, it might necessitate ongoing observation. This is avoided by passive immunization, which delivers exogenous antibodies, but it may necessitate repeated dosage, which raises concerns about treatment burden.

In terms of manufacturing complexity, well-established platforms for the production of monoclonal antibodies are advantageous for passive immunization (ABBV-0805). UB-312 requires peptide synthesis and formulation with adjuvants, while ABBV-0805 relies on established monoclonal antibody manufacturing platforms. However, comparative manufacturing complexity has not been directly evaluated.

Challenges in Translating Preclinical Findings to Clinical Parkinson's Disease

Despite the encouraging results observed in animal models, translating these findings into clinical benefit in Parkinson's disease is challenging. Transgenic and other experimental models reproduce selected features of α-synuclein pathology or motor dysfunction, but they do not fully reproduce the complexity and long-term progression of human Parkinson's disease. For example, the A30P and A53T mouse

models used to evaluate ABBV-0805 involve genetically driven α-synuclein expression and can develop pathology and motor abnormalities that differ in timing, distribution, and biological context from sporadic Parkinson's disease in humans. Similarly, improvements in motor performance or α-synuclein pathology in mice may reflect effects within the experimental model without necessarily indicating that the treatment will slow the clinical progression in human patients.

Heterogeneity/Patient Selection

Parkinson's disease is heterogeneous in terms of clinical and biological terms. Because of this it may complicate the identification of patients most likely to benefit from α-synuclein immunotherapy. Patients can differ in disease stage, rate of progression, genetic background, α-synuclein pathology, motor and non-motor manifestations, and the extent of neuronal loss at treatment initiation. Consequently, an immunotherapy that targets pathological α-synuclein may have a different therapeutic effect depending on whether substantial pathological accumulation and neuronal degeneration have already occurred. Early intervention may theoretically provide a greater opportunity to modify pathological processes before extensive neuronal loss, but this remains a hypothesis that requires prospective clinical validation. Patient selection may therefore require biological biomarkers in addition to conventional clinical diagnosis and disease staging.

Cost-Effectiveness

In practical application, cost will be a determining factor. Longer dosing intervals and the possibility of long-lasting immune memory may make UB-312 more accessible and less expensive overall, even though its initial R&D and manufacturing costs may be higher. Still, specific cost-effectiveness data are required to confirm a net economic benefit. For ABBV-0805, although monoclonal antibody manufacturing platforms are well established, frequent long-term dosing requirements could significantly increase total treatment cost over time.

Conclusion

In Parkinson's disease immunotherapy, UB-312 and ABBV-0805 have demonstrated encouraging preclinical and early clinical potential. Because UB-312 is designed to generate sustained endogenous antibody responses, it may warrant investigation in early-stage disease and prevention-oriented strategies, although clinical evidence supporting these applications remains limited. For advanced cases or symptom control, passive immunization provides controlled administration of preformed antibodies, but the clinical advantages of this approach over active immunization remain to be established. Clinical trials, long-term immune monitoring, and cost-effectiveness analysis should be the topics of future research.

CONCLUSION

By focusing on toxic forms of α-synuclein, this comparison of active immunization therapy (UB-312) and passive immunization therapy (ABBV-0805) vaccination strategies for Parkinson's disease indicates that both approaches have shown promising preclinical potential to influence pathological α-synuclein processes, although their ability to modify disease progression in humans remains unestablished.

According to preclinical results, UB-312 enhanced motor function and successfully decreased oligomeric α-synuclein in several brain regions without inducing neuroinflammation or T-cell infiltration. Similarly, in aggressive transgenic mouse models, ABBV-0805 nearly doubled lifespan, decreased pathological pSer129 levels, and significantly decreased both soluble and insoluble $\alpha - synuclein$ aggregates. In propagation models, it also demonstrated effectiveness in stopping the spread of $\alpha - synuclein$.

These conclusions were corroborated by clinical data, which showed that UB-312 produced strong, dose-dependent antibody responses in healthy adults with good safety. Ex vivo studies verified that ABBV-0805 could interact with pathogenic $\alpha - synuclein$ in human Parkinson's disease brain tissue, and it showed a clean pharmacokinetic and safety profile in humans.

In summary, ABBV-0805 and UB-312 present complementary strategic options—one providing immediate, focused therapy for advanced stages, and the other driving sustained response—though further investigation in human trials remains essential to establish their clinical efficacy and safety. Despite their differences in mechanism, durability, production complexity, and dosing strategy, both approaches have demonstrated encouraging preliminary safety and biological activity.

Ultimately, patient-specific variables like disease stage and risk profile may influence the decision between active and passive immunization. These findings support continued investigation of both approaches and highlight the need for rigorous clinical validation to determine whether either strategy can ultimately provide disease-modifying benefits in Parkinson's disease.

REFERENCES

1. Pang M, Peng R, Wang Y, Zhu Y, Wang P, Moussian B, et al. Molecular understanding of the translational models and the therapeutic potential natural products of Parkinson's disease. Biomedicine & Pharmacotherapy. 2022 Nov;155:113718.

2. National Institute of Neurological Disorders and Stroke. Parkinson's Disease: Challenges, Progress, and Promise | National Institute of Neurological Disorders and Stroke [Internet]. www.ninds.nih.gov. 2023. Available from: https://www.ninds.nih.gov/current-research/focus-disorders/parkinsons-disease-research/parkinsons-disease-challenges-progress-and-promise

3. Johns Hopkins Medicine. Parkinson's Disease Risk Factors and Causes [Internet]. www.hopkinsmedicine.org. 2022. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/parkinsons-disease/parkinsons-disease-risk-factors-and-causes

4. Sonne J, Beato MR. Neuroanatomy, Substantia Nigra. Nih.gov. StatPearls Publishing; 2022.

5. Dopamine | Paris Brain Institute [Internet]. Paris Brain Institute. 2025. Available from: https://parisbraininstitute.org/glossary/dopamine

6. Mayo Clinic. Parkinson's Disease [Internet]. Mayo Clinic. 2024. Available from: https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055

7. NHS. Parkinson's Disease [Internet]. NHS. NHS; 2022. Available from: https://www.nhs.uk/conditions/parkinsons-disease/

8. Parkinson's Foundation. Causes. Parkinson's Foundation [Internet]. 2021; Available from: https://www.parkinson.org/Understanding-Parkinsons/Causes

9. Europe PMC. Europe PMC [Internet]. Europepmc.org. 2016 [cited 2025 Jun 12]. Available from: https://europepmc.org/article/med/17027339

10. Eriksen JL, Wszolek Z, Petrucelli L. Molecular Pathogenesis of Parkinson Disease. Archives of Neurology. 2005 Mar 1;62(3):353.

11. Gandhi S, Wood NW. Molecular pathogenesis of Parkinson's disease. Human Molecular Genetics [Internet]. 2005 Aug 26 [cited 2019 Apr 27];14(18):2749–55. Available from: https://academic.oup.com/hmg/article/14/18/2749/2355831

12. Cleveland Clinic. Parkinson's disease: Causes, Symptoms, Stages, Treatment, Support [Internet]. Cleveland Clinic. 2022. Available from: https://my.clevelandclinic.org/health/diseases/8525-parkinsons-disease-an-overview

13. Pillay P. Parkinsons Disease [Internet]. Dr Prem Pillay. Available from: https://singaporebrain.org/brain/parkinsons-disease/

14. Stern MB. The early treatment of Parkinson's disease: levodopa, dopamine agonists or both. Parkinsonism & Related Disorders. 2000 Nov;7(1):27–33.

15. Olanow CW. The role of dopamine agonists in the treatment of early Parkinson's disease. Neurology. 2002 Feb 1;58(Supplement 1):S33–41.

16. Dopamine Agonists | Parkinson's Foundation [Internet]. www.parkinson.org. Available from: https://www.parkinson.org/living-with-parkinsons/treatment/prescription-medications/dopamine-antagonists

17. Cleveland Clinic. Dopamine agonists: How they affect your brain [Internet]. Cleveland Clinic. 2023. Available from: https://my.clevelandclinic.org/health/treatments/24958-dopamine-agonists

18. Gandhi KR, Saadabadi A. Levodopa (L-Dopa) [Internet]. National Library of Medicine. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482140/

19. Parkinson's and alpha-synuclein - Cure Parkinson's [Internet]. Cure Parkinson's. 2025. Available from: https://cureparkinsons.org.uk/about-parkinsons/the-science-behind-parkinsons/parkinsons-and-alpha-synuclein/

20. Home [Internet]. www.lundbeck.com. Available from: https://www.lundbeck.com/global

21. Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, Sherman H, Yu I, Shah B, et al. Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease. Movement Disorders. 2013 Mar 1;28(6):811–3.

22. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting Alpha-Synuclein as a Therapy for Parkinson's Disease. Frontiers in Molecular Neuroscience. 2019 Dec 5;12.

23. Lashuel HA. Do Lewy bodies contain alpha-synuclein fibrils? and Does it matter? A brief history and critical analysis of recent reports. Neurobiology of Disease. 2020 Jul;141:104876.

24. How A53T Alpha Synuclein Can Affect Parkinson's Disease [Internet]. News-Medical.net. 2020. Available from: https://www.news-medical.net/whitepaper/20200123/How-A53T-Alpha-Synuclein-Can-Affect-Parkinsons-Disease.aspx

25. Temple RC, Mihai AP, Arena DA, Marrows CH. Ensemble magnetic behavior of interacting CoFe nanoparticles. Frontiers in Physics. 2015 Jul 23;3.

26. Whittaker H, Qui Y, Bettencourt C, Houlden H. Structural features of the alpha-synuclein monomer [Figure 1]. In: Multiple system atrophy: Genetic risks and alpha-synuclein mutations [Internet]. ResearchGate; 2017 [cited 2025 Jun 12]. Available from:

https://www.researchgate.net/figure/Structural-features-of-the-alpha-synuclein-monomer-A-structure-of-the-full-length_fig1_321396658

27. Li D, Yau WY, Chen S, Wilton S, Mastaglia F. Monomeric alpha-synuclein (α-Syn) is an intrinsically disordered protein that constantly undergoes transformation into different conformations [Figure 1]. In: A personalised and comprehensive approach is required to suppress or replenish SNCA for Parkinson's disease. *NPJ Parkinsons Dis*. 2025;11:42. Available from: https://www.nature.com/articles/s41531-025-00887-3

28. Lee JS, Lee SJ. Mechanism of Anti-α-Synuclein Immunotherapy. Journal of Movement Disorders. 2016 Jan 25;9(1):14–9.

29. Alfaidi M, Barker RA, Kuan WL. An update on immune-based alpha-synuclein trials in Parkinson's disease. Journal of Neurology. 2024 Dec 12;272(1).

30. Henríquez G, Narayan M. Targeting α-synuclein aggregation with immunotherapy: a promising therapeutic approach for Parkinson's disease. 2023 Aug 25;207–34.

31. Wexler M. Parkinson's vaccine seen to target toxic protein in Phase 1 trial [Internet]. Parkinson's News Today. 2024. Available from: https://parkinsonsnewstoday.com/news/parkinsons-vaccine-targets-toxic-protein-phase-1-trial/

32. Nordström E, Eriksson F, Sigvardson J, Johannesson M, Kasrayan A, Jones-Kostalla M, et al. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiology of Disease. 2021 Dec;161:105543.

33. Chatterjee D, Kordower JH. Immunotherapy in Parkinson's disease: Current status and future directions. Neurobiology of Disease. 2019 Dec;132:104587.

34. Kuo G, Ramhari Kumbhar, Blair W, Dawson VL, Dawson TM, Mao X. Emerging targets of α-synuclein spreading in α-synucleinopathies: a review of mechanistic pathways and interventions. Molecular Neurodegeneration. 2025 Jan 23;20(1).

35. Reddy K, Dieriks BV. Multiple system atrophy: α-Synuclein strains at the neuron-oligodendrocyte crossroad. Molecular Neurodegeneration. 2022 Nov 26;17(1).

36. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathologica. 2021 Nov 6;143(1):55–73.

37. Nimmo JT, Smith H, Wang CY, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2021;143(1):55–73. Figure 1.
38. UB-312 Synuclein Vaccine Safe in Controls. Next Up: Parkinson's. | ALZFORUM [Internet]. Alzforum.org. 2022. Available from: https://www.alzforum.org/news/conference-coverage/ub-312-synuclein-vaccine-safe-controls-next-parkinsons

39. Nordström E, Eriksson F, Sigvardson J, Johannesson M, Kasrayan A, Jones-Kostalla M, et al. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiology of Disease. 2021 Dec;161:105543.

40. Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of ABBV-0805, an Anti-Alpha-Synuclein Monoclonal Antibody in Healthy Subjects - MDS Abstracts [Internet]. MDS Abstracts. 2021 [cited 2025 Jun 15]. Available from: https://www.mdsabstracts.org/abstract/randomized-placebo-controlled-single-ascending-dose-study-to-evaluate-the-safety-tolerability-pharmacokinetics-and-immunogenicity-of-abbv-0805-an-anti-alpha-synuclein-monoclonal-antibody-in-healt/

41. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 2.

42. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 3.

43. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 5.

44. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 6.

45. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 7

46. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 8

47. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 10

48. Nimmo JT, Smith H, Wang CY, Teeling JL, Nicoll JAR, Verma A, et al. Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. Acta Neuropathol. 2022;143(1):55–73. Fig 11

49. Alzforum. UB-312 α-synuclein vaccine is safe, controls next in Parkinson's. Alzforum. 2022 Apr 9 [cited 2025 Jun 16]. Available from: https://www.alzforum.org/news/conference-coverage/ub-312-synuclein-vaccine-safe-controls-next-parkinsons. Fig.

50. Alzforum. UB-312 α-synuclein vaccine is safe, controls next in Parkinson's. Alzforum. 2022 Apr 9 [cited 2025 Jun 16]. Available from: https://www.alzforum.org/news/conference-coverage/ub-312-synuclein-vaccine-safe-controls-next-parkinsons. Fig.

51. Gao X, Smith M, Jones A, et al. ABBV-0805 selectively targets soluble toxic α-synuclein aggregates with a picomolar affinity and demonstrates excellent in vivo efficacy. Neurobiol Dis. 2022;[Epub ahead of print] (Figure 7). Available from: https://ars.els-cdn.com/content/image/1-s2.0-S0969996121002928-gr7.jpg

52. AbbVie and BioArctic. ABBV-0805 selectively targets soluble toxic α-synuclein aggregates with a picomolar affinity and demonstrates excellent in vivo efficacy. Neurobiol Dis. 2021;161:105543. Fig 8. Available from: https://ars.els-cdn.com/content/image/1-s2.0-S0969996121002928-gr8.jpg

53. Nordström E, Eriksson F, Sigvardson J, et al. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiol Dis. 2021;161:105543. Fig 9. Available from: https://ars.els-cdn.com/content/image/1-s2.0-S0969996121002928-gr9.jpg

54. Nordström E, Eriksson F, Sigvardson J, et al. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiol Dis. 2021;161:105543. Fig 10. Available from: https://ars.els-cdn.com/content/image/1-s2.0-S0969996121002928-gr10.jpg

55. Nordström E, Eriksson F, Sigvardson J, Johannesson M, Kasrayan A, Jones-Kostalla M, et al. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiol Dis. 2021 Dec;161:105543. Fig 11. Available from: https://ars.els-cdn.com/content/image/1-s2.0-S0969996121002928-gr11.jpg

56. Eijsvogel P, et al. Target engagement and immunogenicity of an active immunotherapeutic targeting pathological α-synuclein: a phase 1 placebo-controlled trial. Nature Medicine. 2024;30:2631–2640.