A Double-Blind, Randomized, Placebo-Controlled Trial of Ursodeoxycholic Acid (UDCA) in Parkinson's Disease

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ABSTRACT: Background: Rescue of mitochondrial function is a promising neuroprotective strategy for Parkinson's disease (PD). Ursodeoxycholic acid (UDCA) has shown considerable promise as a mitochondrial rescue agent across a range of preclinical in vitro and in vivo models of PD.
Objectives: To investigate the safety and tolerability of high-dose UDCA in PD and determine midbrain target engagement.

Methods: The UP (UDCA in PD) study was a phase II, randomized, double-blind, placebo-controlled trial of UDCA (30 mg/kg daily, 2:1 randomization UDCA vs. placebo) in 30 participants with PD for 48 weeks. The primary outcome was safety and tolerability. Secondary outcomes included 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS) to explore target engagement of UDCA in PD midbrain and assessment of motor progression, applying both the Movement Disorder Society

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Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) and objective, motion sensor-based quantification of gait impairment.

Results: UDCA was safe and well tolerated, and only mild transient gastrointestinal adverse events were more frequent in the UDCA treatment group. Midbrain ^{31}P-MRS demonstrated an increase in both Gibbs free energy and inorganic phosphate levels in the UDCA treatment group compared to placebo, reflecting improved ATP hydrolysis. Sensor-based gait analysis indicated a possible improvement of cadence (steps per minute) and other gait parameters in the UDCA group compared to placebo. In contrast, subjective assessment applying the MDS-UPDRS-III failed to detect a difference between treatment groups.

Conclusions: High-dose UDCA is safe and well tolerated in early PD. Larger trials are needed to further evaluate the disease-modifying effect of UDCA in PD. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Introduction

Mitochondrial dysfunction was first identified in sporadic Parkinson's disease (PD) and has since been implicated in all forms of familial PD.[1,2] Rescue of mitochondrial function has therefore been proposed as a promising neuroprotective strategy.[3,4]

Our group undertook the first screen of an entire compound library in genetically stratified PD patient tissue which led to the identification of the naturally occurring bile acid ursodeoxycholic acid (UDCA) as a promising mitochondrial rescue compound for PD.[5,6] We subsequently confirmed the mitochondrial rescue effect of UDCA in mechanistically stratified sporadic PD patient tissue.[7] Other groups have independently reported a beneficial effect of both UDCA and its taurine conjugate tauroursodeoxycholic acid (TUDCA) in toxin-induced cell culture models as well as in the classical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- and rotenone-induced rodent models of PD.[8-14] UDCA appears to exert its neuroprotective effect via improved mitochondrial function and transport as well as ameliorated autophagic flux, involving the AMPK/mTOR and PINK1/Parkin pathways.[14]

UDCA has been licensed to treat primary biliary cholangitis at the dose of 15 mg/kg for >30 years. Its excellent safety and tolerability profile makes it ideally suited for the drug repurposing strategy.[15,16]

Pharmacokinetic studies in patients with amyotrophic lateral sclerosis (ALS) confirmed blood–brain barrier penetrance of UDCA, especially at higher doses.[17] In 2015, the international Linked Clinical Trials Initiative (iLCT) named UDCA as its most highly prioritized neuroprotective compound for investigation in clinical trials to further validate its neuroprotective potential in PD.

Here we present the results of a phase II, double-blind, randomized, placebo-controlled trial of 30 mg/kg of UDCA in early PD, the UP Study. The primary outcome of our study was safety and tolerability of UDCA in PD. We also applied phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) to provide evidence of mechanistic target engagement for UDCA in PD midbrain tissue, including the substantia nigra as the key site of PD pathology.[18,19] In addition, we combined 'gold standard' clinical rating scales with sensor-based objective gait analysis to explore the effect of UDCA versus placebo on PD motor progression. We also assessed the effect of high-dose UDCA medication on bile acid composition throughout the trial and undertook genetic screening for pathogenic mutations in Mendelian-inherited PD genes and risk variants in *glucocerebrosidase* (*GBA*).

Methods

Study Design and Participants

A comprehensive protocol for this trial has previously been published.[20] The full trial protocol is also provided in Data S1: Supplement 1. In brief, The UP Study (Trial registration: EudraCT no. 2018–001887-46) was a phase II, two-center, double-blind, randomized, placebo-controlled trial of 30 mg/kg of UDCA in recent-onset PD (≤3 years since diagnosis according to Queen Square Brain Bank Criteria) with sustained (>3 months) motor response to dopaminergic medication. UDCA was administered orally for 48 weeks with a subsequent 8-week washout phase to 31 participants with a 2:1 randomization of drug versus placebo. Changes in the dose of the symptomatic dopaminergic medication by the treating physician were permissible. The trial was conducted at two sites – Sheffield Teaching Hospitals (STH) and University College London Hospitals (UCLH) – and was approved by the East of England Ethics Committee (Protocol ID: 18/EE0280). STH acted as sponsor of the study (STH18493). All participants provided written informed consent prior to any study-related activities in accordance with the Declaration of Helsinki.

Following a screening visit to confirm eligibility, participants attended six further visits: baseline (start of

treatment period), weeks 12, 24, 36, 48 (end of treatment period), and week 56 (end of washout period). Treatment with either UDCA or placebo was commenced at a dose of 250 mg per day and increased by 250 mg every 3 days until the target weight-dependant dose of 30 mg/kg was achieved. Placebo and UDCA were provided by PRO.MED.CS Praha a.s. and matched with no identifiable differences in taste, appearance, or smell. PRO.MED.CS Praha a.s. did not have any input into trial design, protocol development, or delivery.

Outcomes

The primary outcome was to compare the safety and tolerability of UDCA at 30 mg/kg to placebo in PD as indicated by the following: number of serious adverse events (SAEs), number of adverse treatment reactions, and number of participants who completed the study. At each visit, safety monitoring was performed, and adverse events (AEs) were reviewed and assessed for severity and likely relationship to UDCA. Compliance was assessed by counting the number of investigational medicinal product (IMP) capsules returned and expressed as (IMP dispensed – IMP returned)/IMP prescribed.

The predefined secondary outcomes included: (1) changes of bioenergetic metabolite estimates derived from ^{31}P-MRS in the midbrain; (2) changes in the supervised gait analysis; and (3) changes in the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III). Changes for all secondary outcomes were assessed from baseline to week 48 in the UDCA versus placebo group, and both the supervised gait analysis and the MDS-UPDRS were undertaken in the practically defined "OFF" medication state.

Exploratory outcomes included the change of MDS-UPDRS-III in the practically defined "OFF" medication state at other time points (weeks 48–56 and baseline to week 56). We also recorded the levodopa equivalent dosage (LED), MDS-UPDRS-I–IV in the "ON" state, Montreal Cognitive Assessment (MoCA), Montgomery–Asberg Depression Rating Scale (MADRS), Non-Motor Symptom Questionnaire (NMSQ), and the 39-item Parkinson's Disease Questionnaire (PDQ-39) quality-of-life questionnaire.[21-26] Whenever COVID-19 restrictions prevented face-to-face review of participants, clinical assessments were conducted remotely over video. A summary of the safety monitoring and clinical assessment study procedures are provided in Figure S1 and Supplement 2.1: Data S2.

Sample Collection, Gait Analysis, and ^{31}P-MRS Imaging

Genetic and bile acid analyses were undertaken in all participants. Further detail is provided in Supplement 2.1 and 2.2. Sensor-based gait analysis was undertaken at the Clinical Research Facility of the STH study site only for STH-recruited participants due to COVID-19.

Gait outcomes included spatiotemporal metrics and gait quality measures related to intensity, regularity and variability.[27-29] The experimental design of the gait analysis is depicted in Data S2: Supplementary Figure 2 with further detail in Supplement 2.3.

All participants in the trial were invited for ^{31}P-MRS scans both at baseline and week 48 at the STH site. Further details of ^{31}P-MRS acquisition and analysis are provided in Figure 1 and Supplement 2.4.

Statistical Analysis

Statistical analyses were by intention-to-treat (ITT). Some assessments were delayed due to the COVID pandemic; sensitivity analyses were performed for each analysis excluding data collected outside of the planned assessment window. All results presented are using the full analysis dataset unless stated otherwise. SAEs and adverse treatment reactions are presented descriptively; in summaries individual AEs (by preferred term) are counted once per participant at the worst severity. We considered the rate of SAEs reported in the exenatide trial in PD to be tolerable and acceptable (ie, 20%). If no SAEs were found in the group receiving UDCA ($n = 20$) then the likelihood that the true SAE rate is less than 20% is 0.990778 (ie, there is a less than 1% chance that the true SAE rate is ≥20%).[30] The study was not powered to detect differences in the secondary or exploratory endpoints and therefore the interpretation of observed differences and confidence intervals (CIs) takes priority over statistical significance conferred by P-values and no adjustment is made for multiple testing.

Demographic and clinical assessment data were summarized using relevant summary statistics. Multivariate statistical analysis of serum bile acid profiling data was performed using SIMCA 17.0 (MKS Umetrics AB) and Pareto-scaled, log-transformed data. Between-group differences for changes in clinical parameters were assessed using t-tests for continuous data. Between-group differences in gait analysis parameters from baseline to week 48 were compared using Mann–Whitney U tests as data did not appear to be normally distributed. The change in ^{31}P-MRS parameters from baseline to week 48 was compared between groups using t-tests for each metabolite in turn with further exploratory analysis using linear regression. Additional information on the statistical analysis is also included in Supplements 2.2–2.4. We also refer to the full Statistical Analysis Plan (SAP, Data S3: Supplement 3); preplanned analysis was carried out using SAS v9.4.

Data Sharing

Raw data are available from the corresponding author on reasonable request.
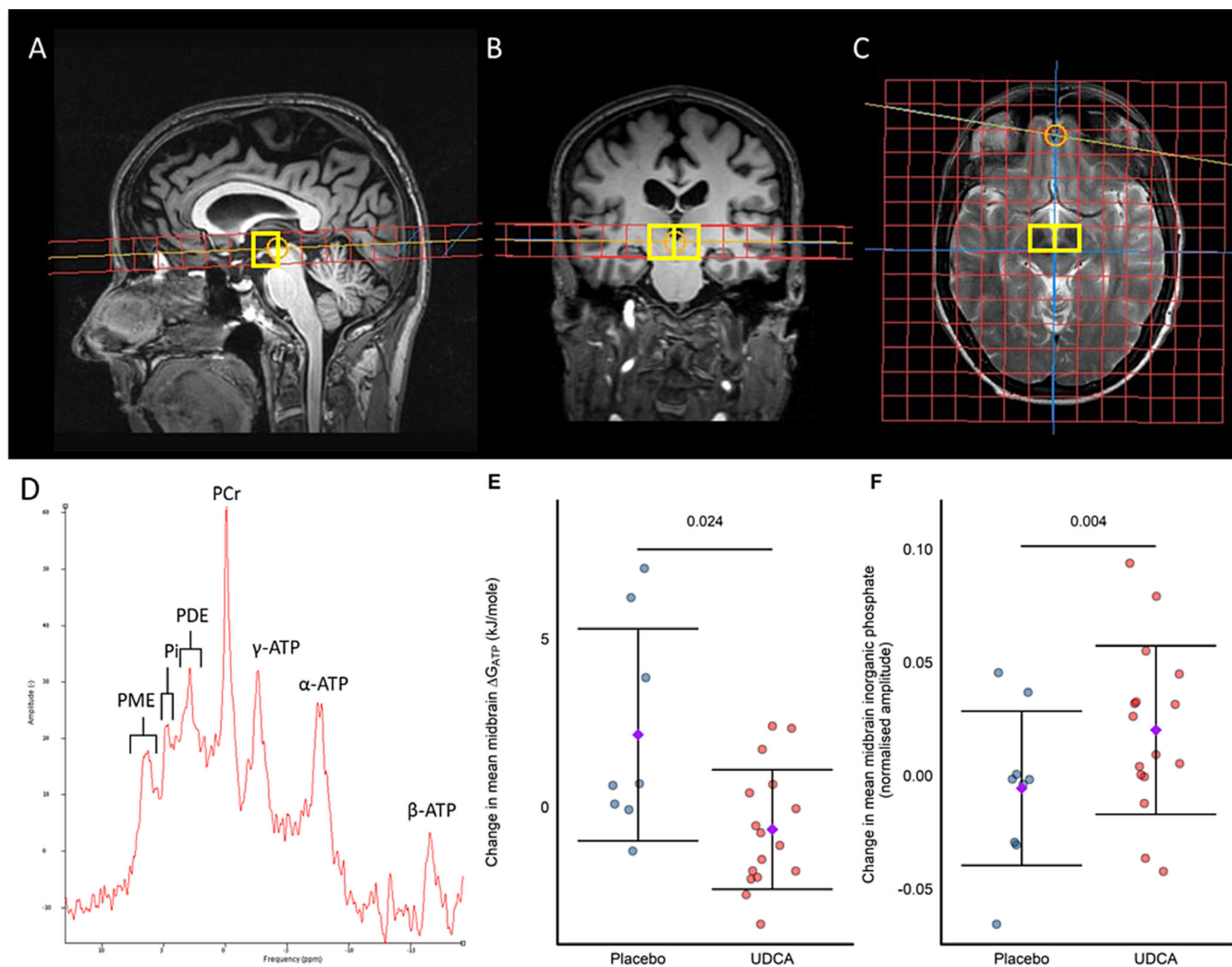
FIG. 1. [31]Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) voxel localization, example spectra, and results. Sagittal (A), coronal (B), and axial (C) images demonstrating spectroscopic grid positioning for the midbrain voxels. (D) Example spectrum obtained from the midbrain of an UP Study participant. Change from baseline to week 48 in key ^{31}P-MRS parameters from the midbrain for (E) ΔG_{ATP} and (F) inorganic phosphate; purple diamond and error bars signify mean $\pm$ standard deviation; *P*-values depicted on each panel above the bar are for the significance of the estimated treatment coefficient with ursodeoxycholic acid (UDCA) as assessed by linear regression. UDCA $n = 16$, placebo $n = 9$ except panel (E) where placebo $n = 8$ due to an excluded magnesium value prior to unblinding required for calculation of ΔG_{ATP}. PME, phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; γ-ATP, gamma adenosine triphosphate; α-ATP, gamma adenosine triphosphate; β-ATP, gamma adenosine triphosphate; ΔG_{ATP}, Gibbs free energy of ATP hydrolysis; UDCA, ursodeoxycholic acid.

Results

Patient Characteristics

A total of 33 participants were assessed for eligibility from January 2019 to October 2019, with 22 participants assessed at STH and 11 at UCLH.[20] Two participants were excluded due to a MoCA score <25. In total 31 participants were randomized, 11 to placebo and 20 to 30 mg/kg of UDCA daily, titrated to target dose over approximately 8 weeks. Full details of cohort enrollment are shown in Figure 2. Demographic and clinical characteristics are summarized in Table 1.

The mean age of the UDCA treatment group was approximately 5 years younger than the mean age of the placebo group (56.3 vs. 61.9 years), prompting us to undertake additional ANCOVA analysis to allow for a possible effect of the lower age in the UDCA treatment group (see later).

Genetic Analysis and Serum Bile Acid Analysis

None of the trial participants carried pathogenic mutations in monogenic PD genes or pathogenic risk variants of *GBA*. Following commencement of treatment with UDCA, marked enrichment for UDCA and its conjugates glycoursodeoxycholic acid (GUDCA) and TUDCA compared to baseline were found at all visits during the treatment period. Bile acid profiles returned
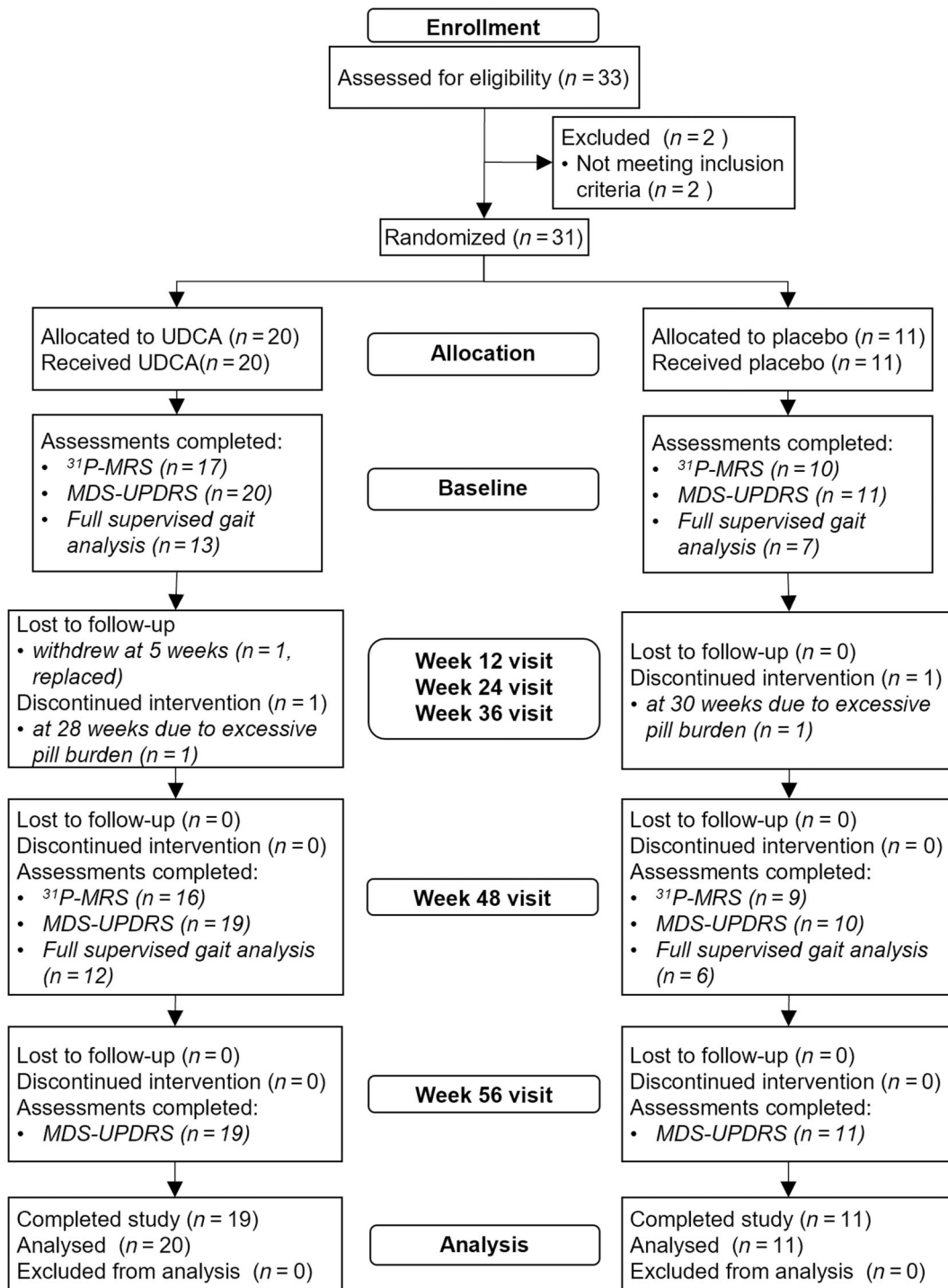
FIG. 2. CONSORT flowchart of enrollment, allocation, and follow-up assessments performed. Analysis used an intention-to-treat population therefore all participants randomized were included in the analysis dataset. Details of key secondary outcome assessments are included to demonstrate data completeness. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; ^{31}P-MRS, phosphorus-31 magnetic resonance spectroscopy; UDCA, ursodeoxycholic acid.

to levels comparable to baseline values at week 56 following the 8-week washout. No changes compared to baseline were seen at any time point in placebo-treated patients. Detailed results of the bile acid analysis are provided in Supplement 2.2 and Data S2: Supplementary Figure 3.

Primary Outcome

One participant withdrew after 5 weeks of treatment due to difficulties swallowing the number of IMP capsules in addition to their regular medication, but not pharmacological side effects of the IMP as such. This

TABLE 1 *Demographic and clinical characteristics*

Characteristic	UDCA (n = 20)	Placebo (n = 11)
Age (years)		
Mean ± SD	56.3 ± 7.6	61.9 ± 8.28
Range	40–74	53–73
Sex (n, %)		
Male	14 (70)	5 (45.5)
Female	6 (30)	6 (54.5)
BMI (kg/m^2)		
Mean ± SD	26.4 ± 3.23	24.9 ± 3.54
Range	20.9–31.8	18.1–32.4
Disease duration (months)		
Mean ± SD	16.3 ± 11.7	22.1 ± 7.2
Range	2.3–41.5	10.7–32.7
Family history of PD in a first-degree relative (n, %)		
Present	1 (5)	2 (18.2)
Absent	19 (95)	9 (81.8)
Modified Hoehn &Yahr (n, %)		
Stage 1	5 (25)	2 (18.2)
Stage 1.5	2 (10)	2 (18.2)
Stage 2	13 (65)	7 (63.6)
Predicted risk of rapid disease progression		
Mean ± SD	0.31 ± 0.16	0.28 ± 0.21
Range	0.09–0.77	0.10–0.69

Note: Summary of demographic and clinical features for trial participants in the UDCA versus placebo arm.
Abbreviations: BMI, body mass index; PD, Parkinson's disease; SD, standard deviation; UDCA, ursodeoxycholic acid.

participant was subsequently replaced. The remaining 30 participants all completed the trial, resulting in a total ITT analysis cohort of 31 trial participants. Two participants stopped taking the IMP early at 28 weeks (UDCA group) and 30 weeks (placebo group), respectively (Fig. 2). Both cited the burden of taking an additional 9–10 tablets in addition to their usual medications. All other trial participants (19/20 in the UDCA group and 9/11 in the placebo group) completed the full treatment period. Compliance was excellent in participants completing the 48-week treatment period (mean ± SD; 97.6 ± 5.4% in UDCA vs. 95.2 ± 8.4% in placebo).

Two SAEs occurred, both in the same participant on placebo, namely retroperitoneal hemorrhage leading to hospital admission and subsequent hospital-acquired pneumonia. Since we found no SAEs in the UDCA group in the full ITT population ($n = 20$), the likelihood that the true SAE rate for UDCA was less than 20% is 0.990778.[30] Twenty-four adverse reactions (ARs) were observed in 14/31 participants (10 UDCA and 4 placebo; Table 2). The most frequent ARs were gastrointestinal symptoms: 5/20 (25.0%) participants on UDCA developed mild diarrhea (ie, not requiring any treatment) with three episodes resolving within 48 h or less; a further two participants had episodes that resolved within 72 h. In the placebo group, 1/11 (9.1%) developed diarrhea that resolved within 24 h. Mild nausea (ie, not requiring any treatment) occurred in 2/20 (10%) of participants taking UDCA; in one participant this episode resolved within 24 h, and in the second participant the nausea was of unspecified duration due to missing data. No other ARs occurred in the UDCA treatment group at a frequency of more than 1 of the 20 participants. Blood monitoring performed at all face-to-face visits revealed no clinically significant changes in any blood tests performed other than one incidental finding of asymptomatic hyperkalemia (5.6 mmol/L), present at baseline prior to commencement of treatment in the UDCA group and one isolated increase in alkaline phosphatase (194 IU/L) after retroperitoneal hemorrhage (week 36, placebo group) with subsequent normalization.

Secondary Outcomes

Evidence of target engagement was assessed using ^{31}P-MRS to determine the effect of the IMP on the bioenergetic profile in the midbrain (including the substantia nigra; Fig. 1A–C). A typical ^{31}P-MRS spectrum is depicted in Figure 1D. In total, 25 participants underwent ^{31}P-MRS before and after treatment (UDCA $n = 16$, placebo $n = 9$). Mean midbrain Gibbs free energy of ATP hydrolysis (ΔG_{ATP}) reduced by -0.672 kJ/mole (95% CI -1.62, 0.277) in the UDCA group, but increased by $+2.145$ kJ/mole (95% CI -0.491, 4.781) in the placebo group from baseline to week 48 (treatment estimate -1.929, 95% CI -3.472, -0.385, $P = 0.024$; Fig. 1E). ΔG_{ATP} reflects the amount of energy released from the hydrolysis of ATP to ADP and Pi. As this reaction is exergonic, the value is negative, with more negative values representing greater amounts of energy released to the tissue examined. The observation of an increase in mean midbrain Pi by $+0.02$ (95% CI 0.00, 0.04) in the UDCA group and reduction by -0.006 (95% CI -0.032, 0.02) in the placebo group (treatment estimate 0.032, 95% CI 0.013, 0.051, $P = 0.004$; Fig. 1F) is in keeping with increased hydrolysis of ATP in the UDCA treatment group. None of the other ^{31}P-MRS-derived parameters changed significantly (Data S2: Supplementary Table 1).

Objectively measured changes in motor impairment before and after treatment using a quantitative

TABLE 2 *Adverse treatment reactions*

System organ class	Adverse treatment reaction[a]	UDCA (n = 20) (n (%))	Placebo (n = 11) (n (%))
Gastrointestinal disorders	Abdominal distension	1 (5.0)	1 (9.1)
	Abdominal pain	1 (5.0)	1 (9.1)
	Constipation	1 (5.0)	1 (9.1)
	Diarrhea	**5 (25.0)**	**1 (9.1)**
	Dry mouth	0 (0.0)	1 (9.1)
	Gastroesophageal reflux disease	0 (0.0)	1 (9.1)
	Nausea	**2 (10.0)**	**0 (0.0)**
	Salivary hypersecretion	1 (5.0)	0 (0.0)
Metabolism and nutrition disorders	Abnormal loss of weight	1 (5.0)	0 (0.0)
Musculoskeletal disorders	Arthralgia	1 (5.0)	0 (0.0)
Nervous system disorders	Parkinson's disease progression	0 (0.0)	1 (9.1)
	Restless legs syndrome	1 (5.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Pruritus	1 (5.0)	0 (0.0)
	Rash	1 (5.0)	0 (0.0)

[a]All participants with at least 28 days exposure to study treatment are listed. Only adverse reactions recorded as having a definite, probable, or possible relationship to trial medication which started on or after first dose are included. Participants are counted once per row but may appear in more than one row. Adverse treatment reactions observed in more than one trial participant are highlighted in bold text.

Abbreviation: UDCA, ursodeoxycholic acid.

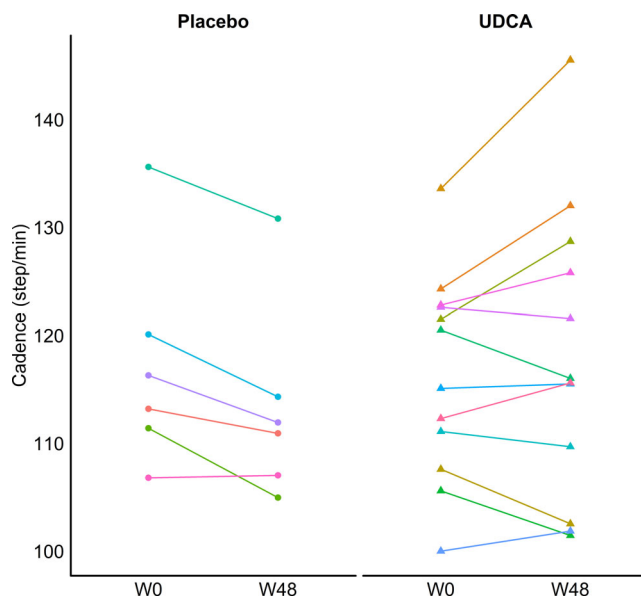supervised, sensor-based gait analysis approach was only available for STH participants due to COVID-19 (12/19 in the UDCA group and 6/11 in the placebo group). Cadence (steps per minute) increased in the UDCA group (median change +1.5 step/min) but decreased in the placebo group between baseline and 48 weeks (median change −4.5 step/min, group-difference $P = 0.0253$; Fig. 3). Of note, there was no correlation between changes in cadence and changes in LED (see Data S2: Supplementary Fig. 4). Additionally, consistent with the improvement in cadence we observed small but significant reductions in absolute stride time and stance time, as well as stride time variability and stance time variability in the UDCA group compared to placebo (see Data S2: Supplementary Fig. 2). The observed changes in gait parameters, while of interest, need to be interpreted with caution due to the small magnitude of changes and overall small cohort size (see Discussion). Further details of the gait analysis results are shown in Supplement 2.3 and Supplementary Table 2.

MDS-UPDRS-III scores in the practically defined "OFF" state improved from baseline to week 48 by a mean of 1.68 points (95% CI −4.90, 1.53) in the UDCA group and by 5.2 points in the placebo group (95% CI −9.82, −0.58) with a mean difference between UDCA and placebo of 3.52 (95% CI −1.83, 8.86, $P = 0.1844$). To investigate any effect of age on these results an ANCOVA model including an age covariate was fitted, with results consistent with the preplanned analysis detailed earlier (mean difference 3.45, 95% CI −2.15, 9.04, $P = 0.2165$).

FIG. 3. Supervised gait analysis. Comparison of changes in cadence from baseline to week 48 (placebo n = 6, ursodeoxycholic acid [UDCA] n = 12). Data are shown at the individual level with each line representing a different participant. Cadence improved in the UDCA group (median change +1.5 step/min) but deteriorated in the placebo group (median change −4.5 step/min). This was significant at the group level ($P = 0.0253$) as assessed with the Mann–Whitney U test.

Exploratory Outcomes

Both the comparison of MDS-UPDRS-III "OFF" scores between week 48 versus week 56 and between baseline versus week 56 were non-significant. The mean MDS-UPDRS-III scores in the "ON" state showed similar patterns from baseline to week 48, weeks 48–56, and baseline to week 56 to those seen in the "OFF" state, again with no significant treatment effect between groups seen at any time point. Changes in LED were not normally distributed, the median change in LED from baseline to week 48 was 0 in both the UDCA group and the placebo group. Eight (40%) patients in the UDCA group had no change in their LED and 7 (64%) in the placebo group also had no change. Of the remaining patients in the UDCA group, 2 (10%) had a reduction in LED, 7 (35%) had an increase and 1 (5%) had missing data; in the placebo group all 4 (36%) remaining patients had an increase in LED.

We observed a small but significant increase in the MADRS scores in the UDCA group compared to placebo from baseline to both week 48 (treatment estimate 2.05 points, 95% CI 0.15, 3.94, $P = 0.0353$) and week 56 (treatment estimate 3.94 points, 95% CI 1.14, 6.74, $P = 0.0075$); however, overall scores remained low in the UDCA group (week 48 mean $\pm$ SD 4.1 ± 4.7 and week 56 mean $\pm$ SD 4.6 ± 5.3) and well below the cut off of 14/15 points likely to indicate a depressive disorder.[31] We also acknowledge the minor worsening in the NMSQ score in the UDCA treatment group from baseline to week 56 (treatment estimate 2.11 points, 95% CI 0.37, 3.84, $P = 0.0193$) but not from baseline to week 48. However, scores at week 56 (mean $\pm$ SD 6.5 ± 4.3) remained consistent with previously reported scores in mild PD (mean $\pm$ SD, 8.0 ± 5.3).[25] These data and all other exploratory clinical outcomes are summarized in Supplement 2.5 and Supplementary Table 3.

Discussion

The UP Study has confirmed that UDCA at a dose of 30 mg/kg is safe and extremely well tolerated in PD with no SAEs and only mild, transient side effects reported in the UDCA treatment group (primary outcome). This is reflected by the high compliance rate (mean of 97.6%) of those participants in the UDCA-treated group who completed the full treatment duration. The lack of clinically significant changes in blood monitoring throughout the trial related to UDCA is also extremely reassuring. This safety profile contrasts with the side effect profile of other recently explored putative neuroprotective compounds.[32,33]

We acknowledge that the excellent safety profile of UDCA in this study needs to be confirmed in larger trials. Although rare SAEs cannot be ruled out, due to the sample size, given the lack of SAEs observed in a sample of 20 UDCA patients the estimated probability of an SAE rate of 14% or more (approximately 1 in 7) in larger trials is less than 5%. Further, high-dose UDCA (≥30 mg/kg daily) has been trialed in other conditions such as ALS and primary sclerosing cholangitis with reassuring safety data in similar sized cohorts.[17,34,35]

Non-significant improvements of MDS-UPDRS-III "OFF" scores over the treatment period were observed in both the UDCA and the placebo group, but were more marked in the placebo group. This is unlikely to be due to changes in dopaminergic medication as the increases in LED over the course of the trial were generally small and similar in both treatment arms. The marked placebo effect may have reduced our ability to detect a clear treatment effect, as observed in other PD neuroprotection trials.[36]

To address the inherent shortcomings of clinical rating scales to quantify motor progression in PD we included supervised, sensor-based objective quantification of motor impairment as a secondary trial outcome. This demonstrated a reduction in cadence and an associated increase in both stride time, stance time, and their variabilities in the placebo treatment group. The longitudinal deterioration of these measures in the placebo group is comparable with previous studies of PD.[37-40] In contrast, we observed either an improvement in the UDCA treatment group or comparatively less worsening in gait over the treatment period. Importantly, this improvement was not correlated with LED. Whilst encouraging, these changes in gait parameters were mostly small, should therefore be interpreted with caution, and need to be validated in larger trials. Changes in MDS-UPDRS-III scores did not correlate with any gait parameters (data not shown), which is not unexpected as only a small proportion of the MDS-UPDRS-III is comprised of comparatively crude gait-related assessments.

Conceptually, the proof of target engagement is a key aspect of early proof-of-concept studies for any compound but has been lacking for many PD neuroprotection studies. Elevated (ie, less negative) ^{31}P-MRS-measured ΔG_{ATP} has previously been observed in mitochondrial cytopathies and is therefore consistent with mitochondrial dysfunction.[41] Administration of coenzyme Q10 in mitochondrial cytopathies resulted in an improvement (lowering) of ΔG_{ATP}, providing evidence of target engagement in muscle tissue.[42] Similarly, the observed lowering of ΔG_{ATP} in the UDCA treatment arm of our study is in keeping with the assumption of mechanistic target engagement for UDCA in the midbrain, resulting in improved mitochondrial function. Sathe and coworkers also reported ^{31}P-MRS-based evidence of target engagement for UDCA in PD in a small, open-label pilot study.[43] However, a different imaging protocol focusing on the occipital cortex was applied, ΔG_{ATP} was not calculated

and only three PD patients had ^{31}P-MRS imaging before and after a 6-week course of UDCA at a dose of 50 mg/kg. Notably, ^{31}P-MRS is also being applied in other completed or ongoing proof-of-concept studies for mitochondrial rescue compounds in PD.[44-46]

There are limitations to our trial. The latter part of our UP Study was compromised by the COVID-19 pandemic. However, our sensitivity analysis of data only collected at the correct time points suggests that this did not have a significant effect on the overall outcome of the trial (data not shown). We excluded PD patients with a more advanced age (>75 years) to limit the impact of additional comorbidities on secondary outcome measures such as the gait analysis. Further, the UDCA treatment group consisted of more males and had a shorter disease duration than the placebo group. Although unlikely, we cannot exclude that these limitations may have impacted secondary outcome results. Additionally, the gait analysis was only conducted in a subset of trial participants due to COVID-related issues; most changes observed were small and await confirmation in larger trials and should therefore be interpreted with caution.

The action of UDCA might be pleiotropic and is yet to be fully elucidated. Changes in the PD gut microbiome are associated with alterations in the bile acid pool.[47] Intriguingly, reductions of (endogenous) UDCA and TUDCA have been reported in an experimental model of prodromal PD; in addition, UDCA treatment partially restores the gut microbial profile in other conditions.[48-50] A beneficial effect of UDCA in PD may therefore not be limited to mitochondrial rescue but also an additional, as yet speculative, effect on the microbiome and the gut–brain axis.

As stated earlier, the UP Study was not formally powered to confirm or refute a neuroprotective effect of UDCA. Subsequent, considerably larger, and more expensive phase IIb/III studies will be required to confirm or refute such a neuroprotective effect for UDCA. However, the excellent safety profile of UDCA at 30 mg/kg, combined with the ^{31}P-MRS-based evidence of target engagement and the promising results from the gait analysis, provide strong rationale for future trials of UDCA in PD and significantly de-risk the required major investment for a definitive study. ∎

Data Availability Statement

Raw data are available from the corresponding author on reasonable request.

References

1. Borsche M, Pereira SL, Klein C, Grunewald A. Mitochondria and Parkinson's disease: clinical, molecular, and translational aspects. J Parkinsons Dis 2021;11(1):45–60.

2. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990;54(3):823–827.

3. Zambrano K, Barba D, Castillo K, et al. Fighting Parkinson's disease: the return of the mitochondria. Mitochondrion 2022;64:34–44.

4. Schapira AH, Olanow CW, Greenamyre JT, Bezard E. Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: future therapeutic perspectives. Lancet 2014;384(9942):545–555.

5. Mortiboys H, Aasly J, Bandmann O. Ursocholanic acid rescues mitochondrial function in common forms of familial Parkinson's disease. Brain 2013;136(Pt 10):3038–3050.

6. Mortiboys H, Furmston R, Bronstad G, Aasly J, Elliott C, Bandmann O. UDCA exerts beneficial effect on mitochondrial dysfunction in LRRK2(G2019S) carriers and in vivo. Neurology 2015;85(10):846–852.

7. Carling PJ, Mortiboys H, Green C, et al. Deep phenotyping of peripheral tissue facilitates mechanistic disease stratification in sporadic Parkinson's disease. Prog Neurobiol 2020;187:101772.

8. Castro-Caldas M, Carvalho AN, Rodrigues E, et al. Tauroursodeoxycholic acid prevents MPTP-induced dopaminergic cell death in a mouse model of Parkinson's disease. Mol Neurobiol 2012;46(2):475–486.

9. Abdelkader NF, Safar MM, Salem HA. Ursodeoxycholic acid ameliorates apoptotic cascade in the rotenone model of Parkinson's disease: modulation of mitochondrial perturbations. Mol Neurobiol 2016;53(2):810–817.

10. Cuevas E, Burks S, Raymick J, et al. Tauroursodeoxycholic acid (TUDCA) is neuroprotective in a chronic mouse model of Parkinson's disease. Nutr Neurosci 2020;25:1–18.

11. Rosa AI, Duarte-Silva S, Silva-Fernandes A, et al. Tauroursodeoxycholic acid improves motor symptoms in a mouse model of Parkinson's disease. Mol Neurobiol 2018;55(12):9139–9155.

12. Moreira S, Fonseca I, Nunes MJ, et al. Nrf2 activation by tauroursodeoxycholic acid in experimental models of Parkinson's disease. Exp Neurol 2017;295:77–87.

13. Chun HS, Low WC. Ursodeoxycholic acid suppresses mitochondria-dependent programmed cell death induced by sodium nitroprusside in SH-SY5Y cells. Toxicology 2012;292(2–3):105–112.

14. Qi H, Shen D, Jiang C, Wang H, Chang M. Ursodeoxycholic acid protects dopaminergic neurons from oxidative stress via regulating mitochondrial function, autophagy, and apoptosis in MPTP/MPP(+)-induced Parkinson's disease. Neurosci Lett 2021;741:135493.

15. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999;354(9184):1053–1060.

16. Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid "mechanisms of action and clinical use in hepatobiliary disorders". J Hepatol 2001;35(1):134–146.

17. Parry GJ, Rodrigues CM, Aranha MM, et al. Safety, tolerability, and cerebrospinal fluid penetration of ursodeoxycholic acid in patients with amyotrophic lateral sclerosis. Clin Neuropharmacol 2010;33(1):17–21.

18. Henchcliffe C, Shungu DC, Mao X, et al. Multinuclear magnetic resonance spectroscopy for in vivo assessment of mitochondrial dysfunction in Parkinson's disease. Ann N Y Acad Sci 2008;1147:206–220.

19. Buckley C, Alcock L, McArdle R, et al. The role of movement analysis in diagnosing and monitoring neurodegenerative conditions: insights from gait and postural control. Brain Sci 2019;9(2):34.

20. Payne T, Sassani M, Buckley E, et al. Ursodeoxycholic acid as a novel disease-modifying treatment for Parkinson's disease: protocol for a two-centre, randomised, double-blind, placebo-controlled trial, the 'UP' study. BMJ Open 2020;10(8):e038911.

21. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating

Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23(15):2129–2170.

22. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25(15):2649–2653.

23. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–699.

24. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389.

25. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 2006;21(7):916–923.

26. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26(5):353–357.

27. Trojaniello D, Ravaschio A, Hausdorff JM, Cereatti A. Comparative assessment of different methods for the estimation of gait temporal parameters using a single inertial sensor: application to elderly, post-stroke, Parkinson's disease and Huntington's disease subjects. Gait Posture 2015;42(3):310–316.

28. Spain RI, St George RJ, Salarian A, et al. Body-worn motion sensors detect balance and gait deficits in people with multiple sclerosis who have normal walking speed. Gait Posture 2012;35(4):573–578.

29. Moe-Nilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. J Biomech 2004;37(1):121–126.

30. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017;390(10103):1664–1675.

31. Leentjens AFG, Verhey FRJ, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. Int J Geriatr Psychiatry 2000;15(7):644–649.

32. Simuni T, Fiske B, Merchant K, et al. Efficacy of nilotinib in patients with moderately advanced Parkinson disease: a randomized clinical trial. JAMA Neurol 2021;78(3):312–320.

33. Pagan FL, Hebron ML, Wilmarth B, et al. Nilotinib effects on safety, tolerability, and potential biomarkers in Parkinson disease: a phase 2 randomized clinical trial. JAMA Neurol 2020;77(3):309–317.

34. Cullen SN, Rust C, Fleming K, Edwards C, Beuers U, Chapman RW. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. J Hepatol 2008;48(5):792–800.

35. Harnois DM, Angulo P, Jorgensen RA, LaRusso NF, Lindor KD. High-dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. Am J Gastroenterol 2001;96(5):1558–1562.

36. Whone A, Luz M, Boca M, et al. Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. Brain 2019;142(3):512–525.

37. Mico-Amigo ME, Kingma I, Heinzel S, et al. Potential markers of progression in idiopathic Parkinson's disease derived from assess-ment of circular gait with a single body-fixed-sensor: a 5 year longitudinal study. Front Hum Neurosci 2019;13:59.

38. Del Din S, Elshehabi M, Galna B, et al. Gait analysis with wearables predicts conversion to parkinson disease. Ann Neurol 2019;86(3):357–367.

39. Hobert MA, Nussbaum S, Heger T, Berg D, Maetzler W, Heinzel S. Progressive gait deficits in Parkinson's disease: a wearable-based biannual 5-year prospective study. Front Aging Neurosci 2019;11:22.

40. Amboni M, Iuppariello L, Iavarone A, et al. Step length predicts executive dysfunction in Parkinson's disease: a 3-year prospective study. J Neurol 2018;265(10):2211–2220.

41. Barbiroli B, Montagna P, Martinelli P, et al. Defective brain energy metabolism shown by in vivo 31P MR spectroscopy in 28 patients with mitochondrial cytopathies. J Cereb Blood Flow Metab 1993;13(3):469–474.

42. Barbiroli B, Iotti S, Lodi R. Improved brain and muscle mitochondrial respiration with CoQ. An in vivo study by 31P-MR spectroscopy in patients with mitochondrial cytopathies. Biofactors 1999;9(2–4):253–260.

43. Sathe AG, Tuite P, Chen C, et al. Pharmacokinetics, safety, and tolerability of orally administered ursodeoxycholic acid in patients with Parkinson's disease-a pilot study. J Clin Pharmacol 2020;60(6):744–750.

44. Prasuhn J, Bruggemann N, Hessler N, et al. An omics-based strategy using coenzyme Q10 in patients with Parkinson's disease: concept evaluation in a double-blind randomized placebo-controlled parallel group trial. Neurol Res Pract 2019;1:31.

45. Schultz JL, Brinker AN, Xu J, et al. A pilot to assess target engagement of terazosin in Parkinson's disease. Parkinsonism Relat Disord 2022;94:79–83.

46. Brakedal B, Dölle C, Riemer F, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metab 2022;34(3):396–407.e6.

47. Li P, Killinger BA, Ensink E, et al. Gut microbiota dysbiosis is associated with elevated bile acids in Parkinson's disease. Metabolites 2021;11(1):29.

48. Graham SF, Rey NL, Ugur Z, et al. Metabolomic profiling of bile acids in an experimental model of prodromal Parkinson's disease. Metabolites. 2018;8(4):71.

49. Li H, Wang Q, Chen P, Zhou C, Zhang X, Chen L. Ursodeoxycholic acid treatment restores gut microbiota and alleviates liver inflammation in non-alcoholic steatohepatitic mouse model. Front Pharmacol 2021;12(1663–9812):788558.

50. Tang R, Wei Y, Li Y, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut 2018;67(3):534–541.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.