Inosine to Increase Serum and Cerebrospinal Fluid Urate in Parkinson Disease
A Randomized Clinical Trial

The Parkinson Study Group SURE-PD Investigators

IMPORTANCE Convergent biological, epidemiological, and clinical data identified urate elevation as a candidate strategy for slowing disability progression in Parkinson disease (PD).

OBJECTIVE To determine the safety, tolerability, and urate-elevating capability of the urate precursor inosine in early PD and to assess its suitability and potential design features for a disease-modification trial.

DESIGN, SETTING, AND PARTICIPANTS The Safety of Urate Elevation in PD (SURE-PD) study, a randomized, double-blind, placebo-controlled, dose-ranging trial of inosine, enrolled participants from 2009 to 2011 and followed them for up to 25 months at outpatient visits to 17 credentialed clinical study sites of the Parkinson Study Group across the United States. Seventy-five consenting adults (mean age, 62 years; 55% women) with early PD not yet requiring symptomatic treatment and a serum urate concentration less than 6 mg/dL (the approximate population median) were enrolled.

INTERVENTIONS Participants were randomized to 1 of 3 treatment arms: placebo or inosine titrated to produce mild (6.1-7.0 mg/dL) or moderate (7.1-8.0 mg/dL) serum urate elevation using 500-mg capsules taken orally up to 2 capsules 3 times per day. They were followed for up to 24 months (median, 18 months) while receiving the study drug plus 1 washout month.

MAIN OUTCOMES AND MEASURES The prespecified primary outcomes were absence of unacceptable serious adverse events (safety), continued treatment without adverse event requiring dose reduction (tolerability), and elevation of urate assessed serially in serum and once (at 3 months) in cerebrospinal fluid.

RESULTS Serious adverse events (17), including infrequent cardiovascular events, occurred at the same or lower rates in the inosine groups relative to placebo. No participant developed gout and 3 receiving inosine developed symptomatic urolithiasis. Treatment was tolerated by 95% of participants at 6 months, and no participant withdrew because of an adverse event. Serum urate rose by 2.3 and 3.0 mg/dL in the 2 inosine groups (P < .001 for each) vs placebo, and cerebrospinal fluid urate level was greater in both inosine groups (P = .006 and <.001, respectively). Secondary analyses demonstrated nonfutility of inosine treatment for slowing disability.

CONCLUSIONS AND RELEVANCE Inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. The findings support advancing to more definitive development of inosine as a potential disease-modifying therapy for PD.

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Author Affiliations: The Parkinson Study Group SURE-PD Investigators are listed at the end of the article.
Corresponding Author: Michael A. Schwarzschild, MD, PhD, Room 3002, MassGeneral Institute for Neurodegenerative Disease, 114 16th St, Boston, MA 02129 (michaels@helix.mgh.harvard.edu).
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Urates is the enzymatic end product of purine metabolism in humans, possesses potent antioxidant and metal chelator properties in vitro,1-2 and confers neuroprotection against oxidative stress-induced dopaminergic neuron death in rodent models of Parkinson disease (PD).3-5 Studies of prospectively followed cohorts identified blood urate level in healthy individuals as an inverse risk factor for PD.6-8 Among iers of prospectively followed cohorts identified blood urate level at baseline predicted slower rates of clinical (disability)10,12 or radiographic (dopamine transporter imaging)13 progression over 2 years. Thus, higher urate level is a predictor of both reduced risk and slower progression of PD.

The convergence of these biological, epidemiological, and clinical data warrants consideration of urate elevation as a potential disease-modifying treatment for PD. Although urate appears to be rapidly degraded within the intestinal tract by bacterial flora, its precursor inosine when taken orally produces a rapid elevation of serum urate.13,14 Long-term inosine treatment in multiple sclerosis cohorts,15-17 comprising mostly women 30 to 50 years old, increased serum urate for 1 or more years with few adverse effects (AEs) other than urolithiasis (which developed in as many as 25% of participants). The older and predominantly male PD population may be more susceptible to AEs of urate elevation, including gout and uric acid urolithiasis (ie, diseases of crystal formation), and possibly cardiovascular, renal, and metabolic disorders.18 Accordingly, we undertook a phase 2 study of oral inosine in early PD with the primary goals of determining its safety, tolerability, and ability to elevate serum and CSF urate levels. Although therapeutically elevation of serum and CSF urate may seem a medical oxymoron, there are many precedents forrationally raising levels of an endogenous factor often viewed as pathogenic (and vice versa). Examples range from raising serum sodium levels to treat orthostatic hypotension (despite their pathogenic role in cardiovascular disease) to raising central nervous system dopamine levels in PD (despite their pathogenic role in various psychotropic disorders). The Safety of Urate Elevation in PD (SURE-PD) trial was designed (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013) with the broader purpose of determining whether and how inosine should be pursued as a urate-elevating strategy in any subsequent phase 3 trials of its disease-modifying potential in PD.

Methods

Details of the trial design are posted19 and to be published (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013) separately and are summarized next.

Participants and Sites

Enrollment criteria were modeled after those of the PRECEPT9 and DATATOP10 trials, in which urate was linked to slower PD progression, except for the following differences: (1) only those individuals whose serum urate level fell below the predicted median of approximately 6 mg/dL (approximately 360 μM) were included, because this subpopulation is at risk of faster disabil-
because of slower than expected enrollment as well as budgetary and statistical considerations (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013). Participants returned 1 month later for a safety visit.

Dose Titration to Serum Urate
Active study drug dosing was adjusted based on serum urate values obtained at study visits 2, 4, 6, 9, and 12 weeks and then 6, 9, 12, 15, 18, and 21 months after randomization (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013). To preserve the blind, serum urate levels (and other potentially discriminating assays) were centrally tested and were available only to an unblinded data manager who directed participant titrations and a Data and Safety Monitoring Committee. Placebo dosing was determined by a titration algorithm intended to match daily capsule intake to that of active drug. Dosing ranged from 1 capsule daily (morning) up to 2 capsules 2 times daily (ie, for a maximum intake of 3.0 g of inosine or lactose per day).

Risk Reduction Measures
In addition to frequent monitoring of serum urate and gradual study drug initiation, we monitored urinary pH, a major determinant of uric acid urolithiasis. Because the effect of inosine on urinary pH was unknown, all participants self-monitored their urinary pH at least daily for the first 12 weeks. Any participant who developed persistently acidic (pH ≤ 5.0) urine implemented a urine alkalinization program with potassium citrate. Urolithiasis prophylaxis was also pursued by encouraging hydration for all participants.

Outcomes

Safety
Prespecified primary outcomes were safety, tolerability, and efficacy of urate elevation. Safety was defined as the absence of serious AEs (SAEs) that warranted terminating an inosine treatment arm or the trial, as determined by the trial’s Data and Safety Monitoring Committee.

Tolerability
Tolerability of the study drug was defined as the extent to which assigned treatment could continue without prolonged dose reduction (>48 consecutive days or >73 cumulative days, which is 10% of total 2-year follow-up) due to AEs and was assessed after 6 and 24 months of receiving the study drug.

Efficacy of Urate Elevation
An inosine treatment was considered effective in elevating urate if either CSF urate levels (measured at the 12-week visit 2.5 hours after the first study drug dose of the day) or serum urate levels (measured as change from baseline) were significantly greater than in the placebo group. A less stringent nonfutility criterion was also specified but was superseded by tests of efficacy.

Secondary Outcomes
Additional outcomes were intended to provide preliminary data to aid the design of a potential phase 3 clinical efficacy trial (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013). These included clinical outcomes based on serial measurements of parkinsonism (Unified Parkinson’s Disease Rating Scale [UPDRS] subscales and determinations of the need for dopaminergic therapy), cognitive function (Montreal Cognitive Assessment), and mood (Geriatric Depression Scale short form).

Statistical Analyses
Safety was assessed by comparing time to first SAE by log-rank test and by comparing overall SAE and AE event rates by Poisson and negative binomial regression, respectively. Proportions of participants tolerant to the study drug at 6 months and 2 years were estimated as Kaplan-Meier product-limit estimates with complementary log-log confidence bounds. Censoring for assessment of tolerability was only due to administrative early stopping of the study drug and thus was reasonably considered noninformative. Serum urate levels were compared using mixed-model analyses of variance with random site-specific intercepts, random participant-specific intercepts and slopes, and treatment-dependent variance heterogeneity. The CSF urate levels were log-transformed and analyzed in a linear model with terms for treatment group, sex, and their interaction. All analyses followed the intention-to-treat principle. Details of methods for secondary analyses are described elsewhere (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013). Analyses were performed using SAS (version 9.3; SAS Institute), and inference was based on 2-tailed tests at α = .05.

Results
Of 164 participants who consented, 75 met eligibility criteria, consistent with the expectation that half of those screened would be excluded because of a serum urate concentration greater than the approximate population median value of 6 mg/dL (Table 1) (Figure 1). Eligible participants were randomized to the 3 treatment groups, which showed similar baseline characteristics (Table 1).

A third (24) of the participants completed 2 years of follow-up, 1 participant withdrew from the study after 9 months (Figure 1), and the remaining 50 concluded follow-up early after 8 to 23 months to complete all follow-up visits by November 2012. All but the 1 participant who withdrew consent completed the safety visit 1 month after study drug discontinuation. Median pre-safety visit follow-up was 18 months.

Safety
Oral inosine dosed to elevate serum urate to the targeted levels appeared safe. A total of 17 SAEs were reported, all after randomization, among 15 participants (Table 2); no participant died. Only musculoskeletal events differed substantially among treatment arms (comparison-wise P = .02), and they occurred only among placebo participants. Similarly, time to first SAE was shorter among placebo participants (eFigure 1 and eTable 1 in Supplement).

Among 259 AEs (including the SAEs) of any type, most were judged mild or unrelated to study medication. Of the 38 AEs that were either moderate or severe in intensity and at least possi-
bly related to the study drug, none showed a statistically significant difference among treatment arms. Analyses of overall AE and SAE rates (eTable 1 in Supplement) also showed no evidence of general safety concerns after 27 876 person-days’ cumulative exposure to inosine at rate-elevating doses (see later).

Some AEs were of specific concern (Table 3), including episodes of symptomatic urolithiasis in 3 participants. These were only reported in women after more than 4 months of receiving the study drug and may have been dose dependent (0, 1, and 2 events in the placebo, mild, and moderate groups, respectively [eTable 1 in Supplement]). Need for alkalinization was rare because urine pH was unaffected by inosine (eTable 2 and eTable 3 in Supplement). Urine collected at each visit was also assessed for the presence of various crystals, and their potential use in monitoring inosine-induced urolithiasis risk was investigated (eTable 4 in Supplement). Although no crystal type was predictive of urolithiasis, uric acid crystals were observed in urine from 10 participants with a dose-dependent distribution (0 placebo, 3 mild, and 7 moderate). The 1 participant who developed a documented symptomatic uric acid stone (after 14 months of inosine in the moderate urate elevation arm) had tested positive for uric acid crystalluria and had relatively low urine pH hovering at 5.5 (just above the trigger for alkalinization). Stones in 2 other participants were likely not uric acid because the composition of one was documented as “65% calcium oxalate dihydrate + 35% carbonate apatite,” and the other though not analyzed was from a participant whose urine pH was around 6.5, which is usually incompatible with uric acid stone formation.

Secondary safety outcomes, including those associated with hyperuricemia, did not differ between treatment groups. For example, serial vital signs, serum assays, and electrocar-
diagrams showed no effect of inosine on blood pressure (eTable 5 and eTable 6 in Supplement), body mass index (eTable 7 in Supplement), serum glucose and cholesterol levels (eTable 8 in Supplement), or electrocardiographic parameters (eTable 9 in Supplement). Similarly, despite the increased frequency of urolithiasis while receiving inosine, there were no other renal SAEs and renal function measures of glomerular filtration rate and serum creatinine remained unchanged from baseline in all groups (data not shown).

**Tolerability**

Inosine as administered was well tolerated (Figure 2A). Five participants (3 randomized to placebo and 2 to mild elevation) permanently discontinued the study drug (Figure 1) and 10 temporo-

### Table 2. Serious AEs in SURE-PD

<table>
<thead>
<tr>
<th>Serious AEs*</th>
<th>No. (%)</th>
<th>Placebo</th>
<th>Ino → Mild</th>
<th>Ino → Mod</th>
<th>Overall</th>
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<td>1 (4)</td>
<td>2 (3)</td>
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<td></td>
</tr>
<tr>
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<td>1 (1)</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
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<tr>
<td>Overall</td>
<td>11 (36)</td>
<td>2 (3)</td>
<td>4 (15)</td>
<td>17 (20)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. AEs of Special Concern in SURE-PD**

<table>
<thead>
<tr>
<th>AEs* of Special Concern</th>
<th>No. (%)</th>
<th>Placebo</th>
<th>Ino → Mild</th>
<th>Ino → Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
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<td>5 (16)</td>
<td>0</td>
<td>1 (4)</td>
<td>6 (7)</td>
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<td>Acute coronary syndrome</td>
<td>1 (4)</td>
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<td>0</td>
<td>1 (1)</td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
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<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Cerebrovascular accident</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
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<td>0</td>
<td>1 (4)</td>
<td>1 (1)</td>
<td></td>
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<tr>
<td>Palpitations</td>
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<td>Goutlike symptoms</td>
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<td>3 (8)</td>
<td>2 (7)</td>
<td>6 (7)</td>
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<tr>
<td>Arthralgia of toe(s)*</td>
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<td>2 (4)</td>
<td>1 (4)</td>
<td>4 (5)</td>
<td></td>
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<tr>
<td>Swelling of toe(s)*</td>
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<td>1 (4)</td>
<td>2 (3)</td>
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<td>Urolithiasis or its symptoms</td>
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<td>2 (2)</td>
<td>2 (2)</td>
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<tr>
<td>Hematuria</td>
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<td>1 (4)</td>
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<tr>
<td>Nephrolithiasis</td>
<td>0</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6 (20)</td>
<td>5 (17)</td>
<td>5 (19)</td>
<td>16 (19)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AE, adverse event; Ino → Mild, inosine dosed to mildly elevate urate; Ino → Mod, inosine dosed to moderately elevate urate; SURE-PD, Safety of Urate Elevation in PD.

*Medical Dictionary for Regulatory Activities system organ class and preferred terms.

*Values show total number of events (% of participants).
rarely suspended the study drug (2 receiving placebo, 3 receiving low inosine, and 5 receiving high inosine), including 1 who ultimately discontinued permanently. Greater than 95% (73) of the 75 participants were tolerant of the study drug at 6 months in all treatment groups, with lower confidence bounds well above the 30% threshold prespecified (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013) for judging a treatment sufficiently tolerable to justify continued study of oral inosine. Kaplan-Meier estimates of 2-year tolerance were greater than 90%, with the lowest observed rate among placebo-treated participants.

Urate Elevation

Participants randomized to mild or moderate elevation treatment arms were titrated to an average inosine dose of 1.18 or 1.51 g/d (The Parkinson Study Group SURE-PD Investigators, unpublished data, 2013) and achieved average increases in serum urate of 2.3 and 3.0 mg/dL, respectively (Figure 2B and eTable 10 and eTable 11 in Supplement; \( P < .001 \)). Serum urate levels were significantly elevated above placebo as soon as the 2-week visit (V01) (Figure 2B). They were relatively constant starting at the 2-week visit among those in the mild elevation group and continued to rise during titration until the 4-week visit (V02) among those in the moderate elevation group. The 12-week visit (V05) was the only one for which participants were asked not to take their study drug beforehand, accounting for the apparent dip in serum urate at the time of this trough measurement. Serum urate had fully reverted to baseline levels by the time of the safety visit, 1 month after discontinuation of the study drug. Increases in serum urate were observed in both women and men, although the increase was slightly greater in women (eFigure 2 in Supplement) consistent with their lower mean baseline values, as expected.

Figure 2. Tolerability of Inosine and Its Effects on Serum and Cerebrospinal Fluid (CSF) Urate Levels

A, Tolerability of the study drug from baseline to drug discontinuation displayed as Kaplan-Meier survival curves over the maximum 2-year period for participants taking placebo or inosine dosed to mildly or moderately raise serum urate. Tick marks indicate censored events (see the Methods section). B, Estimated time course of serum urate levels across study visits with the study drug initiated at the baseline (BL) visit and continued for as long as 24 months (V12) until 1 month before the final (safety) visit (SV). Means and 95% confidence intervals from a mixed model are displayed. For visits V1 to V12, serum was collected after morning study drug intake, except for the "trough" sample at week 12 (V05). The shaded range of serum urate concentrations represents exclusionary values at the screening visits (SC1 and SC2). C, The CSF urate concentrations and ranges (bars, with boxes and dots representing the interquartile and median values, respectively) after 12 weeks of receiving the study drug, \( P < .001 \) for the mild and moderate inosine groups compared with placebo. D, Correlation between CSF and serum urate levels at the 12-week visit for individuals identified by their treatment groups and sex. F indicates female and M, male.
The CSF urate levels were measured once (at the 12-week visit) in 44 of the participants (59%). The others did not consent to lumbar puncture (29%) or lumbar punctures were contraindicated (eg, participants receiving warfarin; 4%) or were attempted but failed (7%). Among those measured, levels were 40% and 50% higher in the mild and moderate elevation treatment groups, respectively, relative to placebo participants ($P = .006$ and $P < .001$, respectively) (Figure 2C and eTable 12 and eTable 13 in Supplement). There was evidence of a difference by sex. The CSF urate levels were lower among female than male placebo participants and were significantly elevated in the active arms relative to placebo only among female participants. Twelve-week serum and CSF urate levels in women and men were modestly correlated ($r = 0.43$) (Figure 2D).

**Secondary Analyses**

Although not powered to determine the effects of inosine on long-term changes in clinical measures, preliminary data were collected. Time to need for dopaminergic therapy, which was the primary end point in DATATOP10 and PRECEPT, was reached in 47 of the randomized participants (63%) during the...
study and did not differ significantly among the treatment groups (Figure 3A and eTable 14 in Supplement).

Plausible efficacy of serum urate elevation to delay symptomatic progression was preliminarily assessed using a futility analysis approach equivalent to that used for the primary analysis in the National Institutes of Health Exploratory Trials in PD (NET-PD) program24-25 except that the active groups were compared with our own placebo group rather than with historical controls as in NET-PD.25 The 2 active groups were compared with a futility boundary calculated as 70% of the estimated progression among our placebo participants over 12 months. Both mild and moderate elevation treatments were nonfutile based on this comparison for 6 parkinsonism (sub)scales (eTable 15 in Supplement) including total UPDRS scores, which worsened at an average rate of 1.7 points/y for participants in the moderate elevation treatment group compared with 4.7 points/y for those receiving placebo (Figure 3B and eTable 15 in Supplement).

To reduce the bias introduced by carrying forward the last UPDRS score for participants who developed a need for dopaminergic treatment before the end of the observation period, we also used 2 random-slopes models with follow-up truncated at the time of dopaminergic therapy initiation: 1 with no treatment × sex interaction but assuming linear trends in symptom scores over time (ie, separate treatment × visit estimates) (Figure 3C and eTable 16 in Supplement) and 1 including sex-specific effects of treatment but assuming linear trends in symptom scores over time (Figure 3D and eTable 17 in Supplement). Like the futility analysis, these complementary approaches suggested attenuated clinical progression with increasing inosine doses, although the treatment differences were not significant.

Because demonstration of disease modification by putative neuroprotectants in PD is simpler when not confounded by symptomatic effects, we estimated the effects of inosine on parkinsonian features and disability during gradual wash-in of the study drug (from baseline to week 12) and abrupt washout (from study drug discontinuation to the safety visit 1 month later). Neither active treatment demonstrated an acute symptomatic change during either wash-in or washout based on UPDRS (parts I-III), Schwab and England, or modified Hoehn and Yahr scores (eTable 18 in Supplement).

There was no evidence of an effect of active treatment on cognitive function as assessed by Montreal Cognitive Assessment Rasch scores26 (eTable 19 in Supplement), although only individuals without dementia were enrolled and the placebo group showed no cognitive decline during the study. Mood as assessed on the Geriatric Depression Scale short form worsened slightly on average during the trial only among placebo participants, suggesting a possible preventive effect on depression of urate-elevating inosine (Figure 3E and eTable 19 in Supplement; comparison-wise P < .001 for each inosine group vs placebo), although only 3 participants had scores outside the normal range by the end of follow-up (2 placebo participants and 1 moderate elevation participant).

Discussion

The results of the SURE-PD trial demonstrate that oral inosine treatment in early PD is clinically safe and tolerable and produces an increase in serum and CSF urate. Participants comprised patients with recently diagnosed PD at greater risk of clinical and radiographic progression of PD based on having a serum urate level less than the population median of 6 mg/dL.11 In this population, we found that treatment with inosine for up to 24 months was clinically safe and well tolerated at doses that elevated serum urate concentrations from a mean of 4.5 mg/dL to 6 to 7 and 7 to 8 mg/dL in the 2 dosing regimens. In observational studies,11,12 these higher but still relatively normal urate levels were predictive of favorable outcomes in PD. The present findings support the development of a more definitive trial to investigate the ability of inosine treatment to slow clinical progression among persons with early PD who have lower urate.

We did not observe any increase in risk of SAEs associated with urate elevation in this population, to our knowledge, the oldest to date to be exposed to long-term urate-elevating treatment. Our data strengthen the evidence against a hypertensive effect of urate elevation by inosine27 and do not support the contention that chronically elevated urate contributes to the hypertensive, hyperglycemic, dyslipidemic, and obesity components of metabolic syndrome,18 or to other cardiovascular disease28 associated with higher urate level. Although overall safety of urate-elevating inosine treatment of 50 participants with an average of 1.5 years appeared at least as good as that of control participants, a small or delayed increase in risk of SAEs related to cardiovascular system remains a possibility.

By contrast, the risk of urate-related crystallopathies increases with increasing urate concentration in blood or urine. Our findings suggest that these risks can be adequately managed for inosine treatment. Although no participant developed gout during the study, symptomatic urolithiasis did occur in 3 inosine-treated participants, one of whom had a documented uric acid stone. Exploratory data suggest that monitoring for both uric acid crystal formation and urine acidity in addition to close monitoring of serum urate level may further reduce the risk of urolithiasis related to inosine treatment.

The results provide proof of principle of the ability of oral inosine to raise urate to concentrations in CSF (>0.50 mg/dL) and serum (>6.0 mg/dL) predictive of slower disease progression in prior studies.11,12 This chronic “target engagement” in relevant peripheral and central nervous system compartments at safe and tolerable doses of inosine greatly strengthens the rationale for conducting disease modification studies using the higher dosing regimen for inosine. Whereas our findings support the safety of raising serum urate elevation to either 6.1 to 7.0 or 7.1 to 8.0 mg/dL, the latter was associated with a slower rate of clinical11,12 and particularly radiographic12 decline in prior PD studies.

Refinements to the dose titration regimen used here should take into account our findings that the extent of the actual urate elevation is influenced by sex and the timing of serum sampling relative to dosing. The capacity to increase urate may be related to sex, with women in our trial having achieved greater increases in both serum and CSF because they had lower values than men at baseline (ie, with women enrolling with mean serum urate levels 0.5 mg/dL lower than those in men, whereas all participants were titrated to the same target ranges). Dosing was tied to urate levels in serum collected at random times after the morning dose. Based on pharmacokinetic data from
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Original Investigation Research

Conclusions

The SURE-PD trial provides strong evidence that long-term administration of oral inosine can be generally safe and well tolerated by patients with early PD and increases both serum and CSF urate levels in a dose-dependent fashion. Secondary analyses suggest that a disease-modifying benefit of inosine is plausible. Together with previous findings, these of the present study support a more definitive trial of inosine as a potential treatment to slow the clinical progression of PD.

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Study concept and design: Schwarzschild, Ascherio, Kieburtz, Macklin.


Analysis and interpretation of data: Schwarzschild, Beal, Cudkowicz, Curhan, Hare, Hooper, Kieburtz, Macklin, Oakes, Rudolph, Shoulson, Tennis.

Drafting of the manuscript: Schwarzschild, Ascherio, Macklin.

Critical revision of the manuscript for important intellectual content: All authors.

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Study supervision: Schwarzschild, Ascherio, Beal, Cudkowicz, Curhan, Hare, Hooper, Kieburtz, Macklin, Oakes, Rudolph, Shoulson, Tennis.


The Parkinson Study Group SURE-PD Investigators: Michael A. Schwarzschild, MD, PhD; Alberto Ascherio, MD, DrPH; M. Flint Beal, MD; Merit E. Cudkowicz, MD; Gary C. Curhan, MD; Joshua M. Hare, MD; D. Craig Hooper, PhD; Karl D. Kieburtz, MD; Eric A. Macklin, PhD; David Oakes, PhD; Alice Rudolph, PhD; Ira Shoulson, MD; Marsha K. Tennis, RN; Alberto J. Espay, MD, MSc; Maureen Gartner, RN, MEd; Albert Hung, MD; PhD; Grace Bwala, MBBS; Richard Lanehan, MD; Elmyra Encarnacion, MD; Melissa Ainslie; Richard Castello; Daniel Togasaki, MD, PhD; Gina Barles; Joseph H. Friedman, MD; Lisa Niles, MS; Julie H. Carter, RN, MN, ANP; Megan Murray, MA; Christopher G. Goetz, MD; Jeana Jaglin, RN, CCRC, Anwar Ahmed, MD; David S. Russell, MD, PhD; Candace Cotto, RN; John L. Goudreau, DO, PhD; Doozie Russell; Sofiros Andreas Parashos, MD, PhD; Patricia Ede, RN; Marie H. Saint-Hilaire, MD; Cathi-Ann Thomas, RN, MS; Raymond James; Mark A. Stacy, MD; Julia Johnson, MD; Lisa Gauger, BA; J. Antonnele de Marcada, MD; Sheila Thurlow, MSA, BSN; Stuart H. Isaacson, MD; Lisbeth Carvajal, Jayaraman Rao, MD; Maureen Cook, RN, BSN; Charliese Hope-Porche, RN; Lauren McClurg; Daniela L. Grasso; Robert Logan, MS; Constance Orme, BA; Toi Ross; Alicia F. D. Brocht; Radu Constantinescu, MD; Saloni Sharma, MBBS; Charles Venuto, PharmD; Joseph Weber, Ken Eaton.

The Parkinson Study Group SURE-PD Investigators: Massachusetts General Hospital, Boston, Massachusetts (Schwarzchild, Cudkowicz, Macklin, Hung, Bwala); Harvard School of Public Health, Boston, Massachusetts (Ascherio); Cornell University, New York, New York (Beal); Brigham and Women's Hospital, Boston, Massachusetts (Cudkowicz); University of Miami, Miami, Florida (Hare); Thomas Jefferson University, Philadelphia, Pennsylvania (Hooper); University of Rochester, Rochester, New York (Kieburtz, Oakes, Rudolph); Georgetown University, Washington, DC (Shoulson); Peterborough, New Hampshire (Tennis); University of Cincinnati, Cincinnati, Ohio (Espay, Gartner); Scott & White Memorial Hospital/Texas A&M University, Temple (Lenehan, Encarnacion, Ainslie, Castillo); University of Southern California, Los Angeles (Togasaki, Barles); Butler Hospital, Providence, Rhode Island (Friedman, Niles); Oregon Health & Science University, Portland (Carter, Murray); Rush University Medical Center, Chicago, Illinois (Goetz, Jaglin); Cleveland Clinic, Cleveland, Ohio (Ahmed); Institute of Neurodegenerative Disorders, New Haven, Connecticut (D. S. Russell, Cotto); Michigan State University, East Lansing (Goudreau, D. Russell); Struthers Parkinson's Center, Golden Valley, Minnesota (Parashos, Ede); Boston University, Boston, Massachusetts (Saint-Hilaire, Thomas, James), Duke University, Durham, North Carolina (Stacy, Johnson, Gauger); Eastern Connecticut Neurology Specialists, Manchester (Antonnele de Marcada, Thurlow); Parkinson's Disease & Movement Disorder Center of Boca Raton, Boca Raton, Florida (Isaacson, Carvajal); Ochsner Clinic Foundation, New Orleans, Louisiana (Rao, Cook, Hope-Porche), Administrative Coordination Center, Massachusetts General Hospital, Boston (McClurg, Grasso, Logan); Clinical Coordination Center, University of Rochester, Rochester, New York (Orme, Ross, Brocht, Constantinescu, Sharma, Venuto, Weber, Eaton).

Conflict of Interest Disclosures: None of direct relevance to the drug development of inosine, the potential therapy under study. Note that in accordance with conflict of interest policy of Parkinson Study Group (http://www.parkinson-study-group.org/parkinson-research/constitution-and-bylaws), all SURE-PD steering committee members, site investigators, and site coordinators should have no financial relationship with any involved company during the study. Although the study received no commercial support, Kyowa Hakko USA Inc, its affiliate Kyowa Pharmaceutical Inc, and their parent company Kyowa Hakko Kirin Co Ltd were designated as the only “involved companies.” The designations were based on the use of Kyowa Hakko USA Inc as the supplier from which inosine was obtained (as the active pharmaceutical ingredient for study drug manufacture) through an analyses that incorporated UPDRS data over 2 years in SURE-PD corroborate the suggestion of a dose-dependent attenuation of clinical decline by inosine. Data on time to disability did not indicate delayed disability among participants receiving inosine, although power for this secondary analysis was minimal. Interestingly, treatment with inosine appeared to prevent slight worsening of depressive symptoms during the trial, a finding that if substantiated could strengthen the long-standing theory and early evidence of enhanced motivation as the basis for urate elevation during human evolution.
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REFERENCES


