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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rate is the enzymatic end product of purine metabolism in humans, possesses potent antioxidant and metal chelator properties in vitro,2,3 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 1604 patients with early PD enrolled in the PRECEPT9 and DATATOP10 trials, higher serum11,12 or cerebrospinal fluid (CSF)12 urate levels at baseline predicted slower rates of clinical (disability)11,12 or radiographic (dopamine transporter imaging)10 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 goal of determining its safety, tolerability, and ability to elevate serum and CSF urate levels. Although therapeutically elevated serum and CSF urate may seem a medical oxymoron, there are many precedents for rationally 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 psychotic 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.

Intervention, Dose Titration, and Follow-up
Eligible participants were randomized at their baseline visits in a 1:1:1 distribution to 3 treatment groups: (1) placebo, (2) inosine titrated to mildly elevate serum urate (to 6.1-7.0 mg/dL), and (3) inosine titrated to moderately elevate serum urate (to 7.1-8.0 mg/dL). Treatments constituted oral administration of white opaque gelatin capsules containing 500 mg of the study drug: inosine (active drug) or lactose (placebo).

Initiation, Maintenance, and Discontinuation of Dosing
Treatment was initiated gradually with 1 capsule taken 2 times daily for 2 weeks. After the 2- and 4-week visits, participants received up to 2 capsules 2 and 3 times daily, respectively, as algorithmically determined by serum urate concentration and treatment group assignment. Scheduled discontinuation of the study drug occurred after 24 months (or at the 9- to 21-month visit for those who had not reached 24 months of follow-up in the fall of 2012 at the time of administrative trial termination.
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 urine pH was unknown, all participants self-monitored their urine 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] subscales24 and determinations of the need for dopaminergic therapy), cognitive function (Montreal Cognitive Assessment),22 and mood (Geriatric Depression Scale short form).23

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.11,12 (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-
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 tempo-

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

<table>
<thead>
<tr>
<th>Serious AEsa</th>
<th>No. (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Human ehrlichiosis</td>
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</tr>
<tr>
<td>Pneumonia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Urosepsis</td>
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</tr>
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</table>

**Injury**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ino→ Mild</th>
<th>Ino→ Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical fracture</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>4 (16)</td>
<td>0</td>
<td>0</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3 (12)</td>
<td>0</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Synovial cyst</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Suicide ideation</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (1)</td>
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</table>

**Renal**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ino→ Mild</th>
<th>Ino→ Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (1)</td>
</tr>
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</table>

**Respiratory**

<table>
<thead>
<tr>
<th></th>
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<th>Ino→ Mild</th>
<th>Ino→ Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary fibrosis</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
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</table>

**Overall**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ino→ Mild</th>
<th>Ino→ Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (36)</td>
<td>2 (8)</td>
<td>4 (15)</td>
<td>17 (20)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>AEs of Special Concern</th>
<th>No. (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Goutlike symptoms</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Arthralgia of toe(s)c</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Swelling of toe(s)d</td>
<td>0</td>
</tr>
<tr>
<td>Urolithiasis or its symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>0</td>
</tr>
</tbody>
</table>

**Overall**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ino→ Mild</th>
<th>Ino→ Mod</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (20)</td>
<td>5 (17)</td>
<td>5 (19)</td>
<td>16 (19)</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.

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

b 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.
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 DATATOP$^9$ and PRECEPT,$^9$ 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 symp-
tomatic progression was preliminarily assessed using a futility
analysis approach equivalent to that used for the primary analy-
sis in the National Institutes of Health Exploratory Trials in PD
(NET-PD) program24-25 except that the active groups were com-
pared 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 progress-
ion 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 Supple-
ment) including total UPDRS scores, which worsened at an aver-
age rate of 1.7 points/y for participants in the moderate eleva-
tion 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 dopa-
minergic 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 treat-
ment × sex interaction but allowing unstructured profiles 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 attenu-
ated clinical progression with increasing inosine doses, al-
though the treatment differences were not significant.

Because demonstration of disease modification by puta-
tive 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 wash-
out (from study drug discontinuation to the safety visit 1 month
later). Neither active treatment demonstrated an acute symp-
tomatic 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 cog-
nitive function as assessed by Montreal Cognitive Assessment
Rasch scores26 (eTable 19 in Supplement), although only individu-
als 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 aver-
age during the trial only among placebo participants, suggesting
a possible preventive effect on depression of urate-elevating ino-
sine (Figure 3E and eTable 19 in Supplement; comparison-wise
P < .001 for each inosine group vs placebo), although only 3 par-
ticipants 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 pro-
duces an increase in serum and CSF urate. Participants com-
prised patients with recently diagnosed PD at greater risk of clin-
cal and radiographic progression of PD based on having a serum
urate level less than the population median of 6 mg/dL.11,12 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 observa-
tional studies,11,12 these higher but still relatively normal urate
levels were predictive of favorable outcomes in PD. The pres-
et findings support the development of a more definitive trial
to investigate the ability of inosine treatment to slow clinical pro-
gression 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 treat-
ment. Our data strengthen the evidence against a hyperten-
sive effect of urate elevation by inosine27 and do not support
the contention that chronically elevated urate contributes to
the hypertensive, hyperglycemic, dyslipidemic, and obesity com-
ponents 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
for 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 the cardiovascular system remains a possibility.

By contrast, the risk of urate-related crystallopathies in-
creases with increasing urate concentration in blood or urine.
Our findings suggest that these risks can be adequately man-
aged for inosine treatment. Although no participant devel-
oped gout during the study, symptomatic urolithiasis did oc-
cur in 3 inosine-treated participants, one of whom had a
documented uric acid stone. Exploratory data suggest that moni-
toring 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 dos-
ing 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 sam-
ping 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
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
Inosine to Increase Urate in Parkinson Disease

**ARTICLE INFORMATION**

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**Author Contributions:** Drs Macklin and Schwarzschild had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**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.

**Statistical analysis:** Macklin.

**Obtaining funding:** Schwarzschild, Ascherio, Kieburtz, Macklin.


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**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 as the supplier from which inosine was obtained (as the active pharmaceutical ingredient for study drug manufacture) through an analysis 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.

**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.
unsubsidized retail purchase. All authors provided signed attestation annually that they have no financial relationship with any involved company during the study, except that Dr Stacy indicated in 2013 that in 2012 he renewed a consulting relationship with Kyowa Hakko Kirin Co Ltd over a drug (istradefylline) intended to treat PD that is otherwise unrelated to inosine. Dr Goetz reports consulting and advisory board membership with honoraria from ADP Orphan, Adexx Pharma, Advanced Studies of Medicine, Boston Scientific, CHDI, Health Advances, ICON Clinical Research, Ingenix (i3 Research), National Institutes of Health, Neurorine, Oxford Biomedica, and Synthecins. He received grants/research funding from the National Institutes of Health and the Michael J. Fox Foundation for Parkinson’s Research (MUFF). Dr Goetz directs the Rush Parkinson’s Disease Research Center that receives support from the Parkinson’s Disease Foundation. He directs the translation program for the Movement Disorder Society-sponsored revision of the UPDRS and the Unified Dyskinesia Rating Scale and receives funds from the Movement Disorder Society for this effort. He also received honoraria from the Movement Disorder Society. American Academy of Neurology, University of Pennsylvania, University of Chicago, and University of Luxembourg. He has received royalties from Oxford University Press, Elsevier Publishers, and Wolters Kluwer Health Lippincott, Williams and Williams. No other disclosures were reported.

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