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Adjunctive Lumateperone 42 mg Treatment in Major Depressive Disorder: Efficacy Across Patient-Reported Depression Symptoms

Rakesh Jain, MD[1]; Suresh Durgam, MD[2]; Willie R. Earley, MD[3]; Susan G. Kozauer, MD[2]; Changzheng Chen, PhD[3]

[1]Department of Psychiatry, Texas Tech University School of Medicine – Permian Basin, Midland, TX, USA; [2]Former employee of Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA; [3]Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA

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Background

- Major depressive disorder (MDD) is a complex mental illness characterized by heterogeneous and highly burdensome symptoms[1,2]
- In research and clinical practice, it is important to assess the patient's perspective of symptom burden through patient-reported outcome tools, such as The Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) scale[3,4]
 - This validated tool allows patients to rate the severity of their depression symptoms over multiple symptom domains[4,5]
- Many patients, particularly those with anxious distress, experience ongoing symptoms despite treatment with antidepressant therapy (ADT), highlighting the need for treatments that reduce symptom severity across a range of symptom domains in MDD[2,6]
- Lumateperone is an atypical antipsychotic indicated for the treatment of MDD in adults as adjunct to ADT; the treatment of schizophrenia in adults; and the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate[7]
 - Lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, a D1 receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor[8]
 - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- In a positive, Phase 3, randomized, double-blind, placebo-controlled trial (Study 501 [NCT04985942]), adjunctive lumateperone 42 mg demonstrated significant improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) Total score versus adjunctive placebo at Day 43 and was generally well tolerated in patients with MDD with inadequate ADT response[9]
 - Additionally, patients treated with lumateperone + ADT vs placebo + ADT reported significant improvement in QIDS-SR-16 Total score at Day 43
- In this post hoc analysis of Study 501, the efficacy of lumateperone 42 mg + ADT vs placebo + ADT was evaluated across the QIDS-SR-16 symptom domains in patients with MDD with inadequate ADT response in the overall population and within clinical subgroups

Methods

- Eligible adults (aged 18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 ADTs in the current depressive episode (<50% improvement on the Antidepressant Treatment Response Questionnaire) and had MADRS Total score ≥24, Clinical Global Impression-Severity score ≥4, and QIDS-SR-16 Total score ≥14
- Patients were randomized (1:1) to receive 6-week lumateperone 42 mg or placebo adjunctive to ADT
- A prespecified analysis measured change from baseline to Day 43 in QIDS-SR-16 Total score using an analysis of covariance (ANCOVA) in the intent-to-treat (ITT) population
- This post hoc analysis measured change from baseline to end of treatment (EOT) of the 9 mutually exclusive QIDS-SR-16 domain scores, using an ANCOVA in the overall ITT population and within patient subgroups according to baseline disease characteristics (DSM-5–defined anxious distress [yes vs no] and disease severity [MADRS Total score <32 vs ≥32])
- The 16 QIDS-SR-16 items correspond with the 9 DSM-5 symptom domains used as the diagnostic criteria for MDD[2,3] (**Figure 1**)
 - For each QIDS-SR-16 item, symptom severity was reported on a scale from 0 to 3, with higher scores indicating more severe depression symptoms[3]
 - For the 3 symptom domains comprising >1 QIDS-SR-16 item (i.e., sleep disturbance, appetite/weight change, and psychomotor agitation/retardation), the domain score was defined as the highest observed score across all included items[3]

Figure 1. DSM-5 MDD Symptom Criterion Domains and Corresponding QIDS-SR-16 Items[2,3]

DSM-5 MDD Symptom Criterion Domains	QIDS-SR-16 Items
Sleep disturbances	Highest score of: 1. Falling asleep 2. Sleep during the night 3. Waking up too early 4. Sleeping too much
Sad mood	5. Feeling sad
Decrease/increase in appetite/weight	Highest score of: 6. Decreased appetite 7. Increased appetite 8. Decreased weight 9. Increased weight
Concentration	10. Concentration/decision making
Self-criticism	11. View of myself
Suicidal ideation	12. Thoughts of death or suicide
Interest	13. General interest
Energy/fatigue	14. Energy level
Psychomotor agitation/retardation	Higher score of: 15. Feeling slowed down 16. Feeling restless

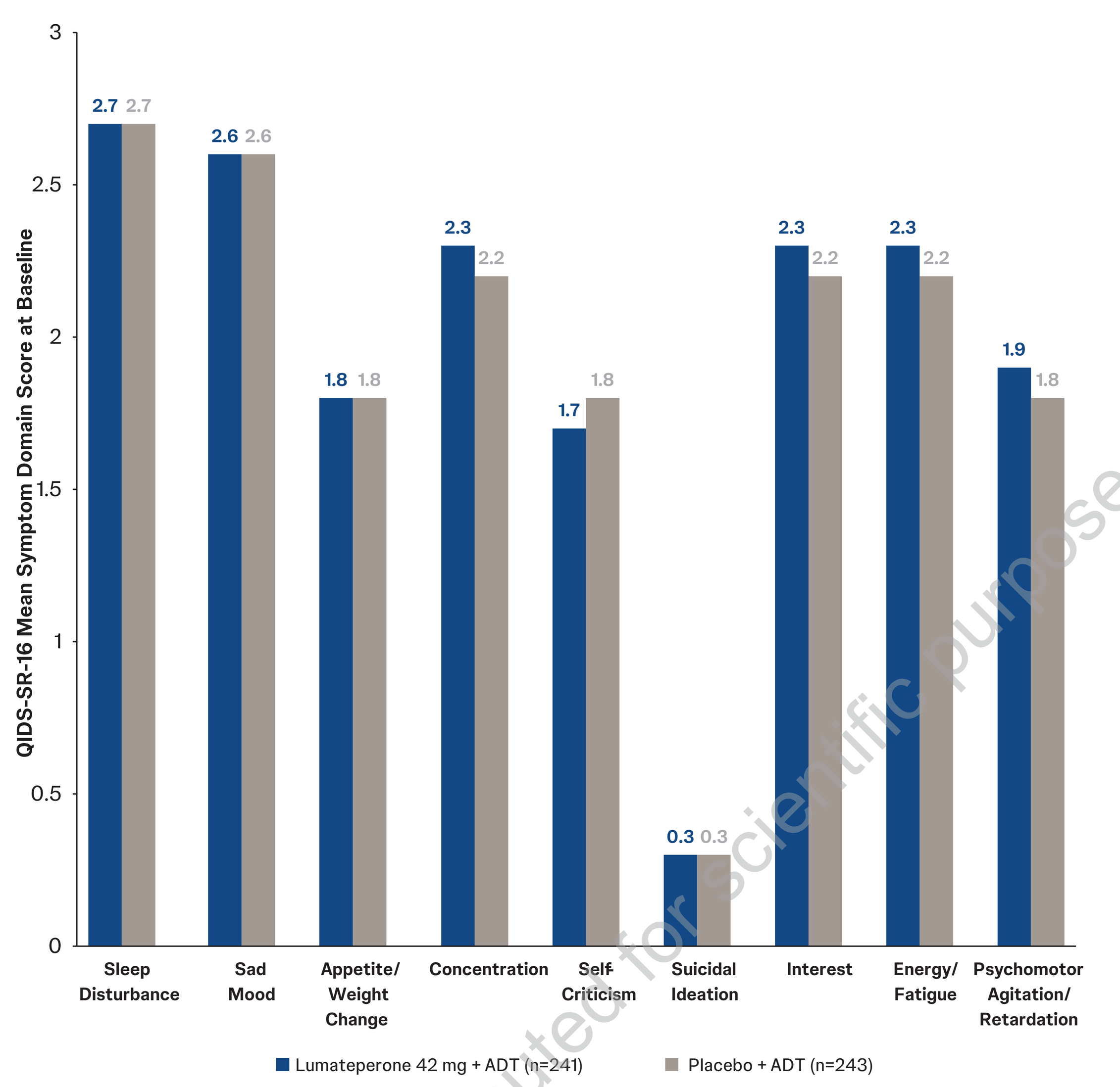
DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MDD, major depressive disorder; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Results

Overall Population

- Of 484 patients in the ITT population (lumateperone + ADT, n=241; placebo + ADT, n=243), 93.4% (n=452) completed treatment
- Baseline characteristics were similar between treatment arms[9]
 - Overall, the mean patient age was 45 years; most patients were female (65.7%) and White (76.7%)
- Lumateperone + ADT significantly improved QIDS-SR-16 Total score vs placebo + ADT from baseline to Day 43 (least squares mean difference vs placebo [LSMD], −2.4; effect size [ES], −0.50; *P*<.0001)[9]
- Baseline QIDS-SR-16 symptom domain scores were balanced between treatment groups, with patients reporting the greatest symptom severity in the domains of sleep disturbance, sad mood, concentration, interest, and energy/fatigue (**Figure 2**)

Figure 2. QIDS-SR-16 Symptom Domain Scores at Baseline (ITT Population)

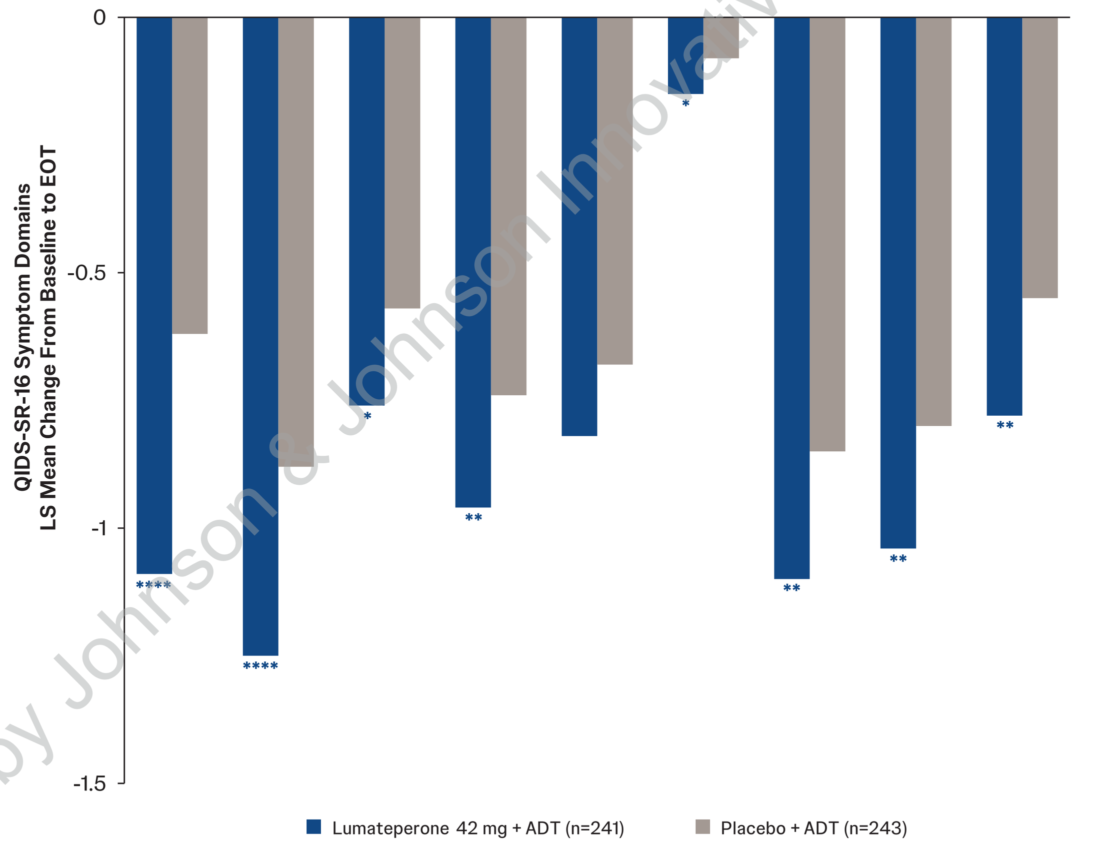

QIDS-SR-16 Mean Symptom Domain Score at Baseline
3
2.5
2
1.5
1
0.5
0
2.7 2.7
2.6 2.6
1.8 1.8
2.3 2.2
1.7 1.8
0.3 0.3
2.3 2.2
2.3 2.2
1.9 1.8
Sleep Disturbance
Sad Mood
Appetite/ Weight Change
Concentration
Self-Criticism
Suicidal Ideation
Interest
Energy/ Fatigue
Psychomotor Agitation/ Retardation
Lumateperone 42 mg + ADT (n=241)
Placebo + ADT (n=243)

ADT, antidepressant therapy; ITT, intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

- From baseline to EOT, 8 of the 9 QIDS-SR-16 symptom domain scores significantly improved with lumateperone + ADT vs placebo + ADT (**Figure 3**)
 - Significance was not reached for the change in symptom severity for the domain of self-criticism (*P*=.065)

Figure 3. Change From Baseline to EOT in QIDS-SR-16 Symptom Domain Scores (ITT Population)

	Sleep Disturbance	Sad Mood	Appetite/ Weight Change	Concentration	Self-Criticism	Suicidal Ideation	Interest	Energy/ Fatigue	Psychomotor Agitation/ Retardation
Effect Size	−0.55	−0.44	−0.22	−0.28	−0.17	−0.19	−0.29	−0.29	−0.30
LSMD	−0.47	−0.36	−0.19	−0.22	−0.15	−0.07	−0.25	−0.24	−0.23
Mean Baseline Score	2.7 2.7	2.6 2.6	1.8 1.8	2.3 2.2	1.7 1.8	0.3 0.3	2.3 2.2	2.3 2.2	1.9 1.8


QIDS-SR-16 Symptom Domains LS Mean Change From Baseline to EOT
0
-0.5
-1
-1.5

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Lumateperone 42 mg + ADT (n=241)
Placebo + ADT (n=243)

*P<.05 **P<.01 ****P<.0001. ANCOVA in the ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; EOT, end of treatment; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

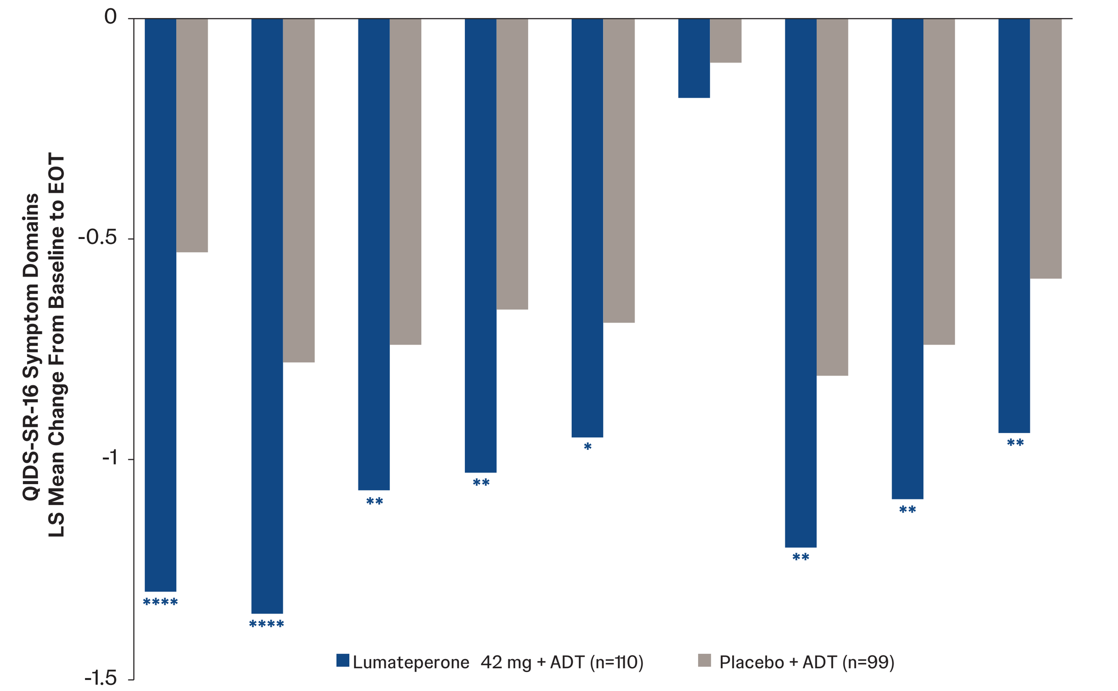
Subgroup Analyses

- At EOT, lumateperone + ADT significantly improved 8 of 9 QIDS-SR-16 symptom domains in patients with DSM-5–defined anxious distress (**Figure 4A**)
 - Numerical improvement in symptom domain scores occurred in those without anxious distress, although results were only significant for sleep disturbance (**Figure 4B**)
- In patients with baseline MADRS Total score <32, lumateperone + ADT significantly improved 6 QIDS-SR-16 symptoms domain scores (sleep disturbance, sad mood, concentration, suicidal ideation, interest, and psychomotor agitation/retardation; [*P*<.05]) from baseline to EOT
 - Patients with baseline MADRS Total score ≥32 had significant improvement (*P*<.05) with lumateperone + ADT at EOT in the QIDS-SR-16 symptom domain scores for sleep disturbance, sad mood, concentration, energy/fatigue, and psychomotor agitation/retardation

Figure 4. Change From Baseline to EOT in QIDS-SR-16 Symptom Domain Scores in Patient Subgroups per Presence/Absence of Anxious Distress at Baseline (ITT Population)

A. Patients With Anxious Distress

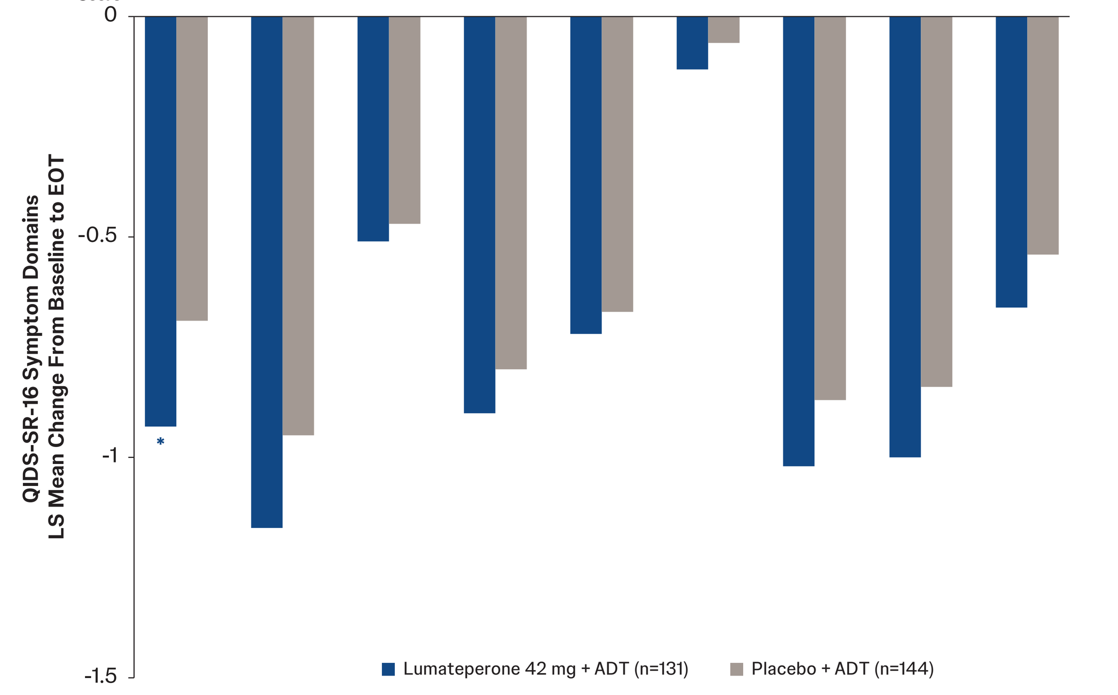
	Sleep Disturbance	Sad Mood	Appetite/ Weight Change	Concentration	Self-Criticism	Suicidal Ideation	Interest	Energy/ Fatigue	Psychomotor Agitation/ Retardation
Effect Size	−0.91	−0.69	−0.39	−0.47	−0.30	−0.21	−0.45	−0.43	−0.47
LSMD	−0.76	−0.58	−0.33	−0.37	−0.26	−0.08	−0.39	−0.36	−0.35
Mean Baseline Score	2.8 2.8	2.7 2.6	1.8 1.8	2.4 2.3	1.9 2.0	0.4 0.3	2.4 2.3	2.3 2.2	2.0 1.9


QIDS-SR-16 Symptom Domains LS Mean Change From Baseline to EOT
0
-0.5
-1
-1.5

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Lumateperone 42 mg + ADT (n=110)
Placebo + ADT (n=99)

B. Patients Without Anxious Distress

	Sleep Disturbance	Sad Mood	Appetite/ Weight Change	Concentration	Self-Criticism	Suicidal Ideation	Interest	Energy/ Fatigue	Psychomotor Agitation/ Retardation
Effect Size	−0.28	−0.24	−0.05	−0.13	−0.06	−0.17	−0.16	−0.19	−0.17
LSMD	−0.24	−0.20	−0.05	−0.11	−0.05	−0.06	−0.14	−0.16	−0.13
Mean Baseline Score	2.7 2.7	2.6 2.6	1.8 1.7	2.2 2.2	1.6 1.7	0.2 0.3	2.3 2.2	2.2 2.2	1.8 1.8


QIDS-SR-16 Symptom Domains LS Mean Change From Baseline to EOT
0
-0.5
-1
-1.5
*
Lumateperone 42 mg + ADT (n=131)
Placebo + ADT (n=144)

*P<.05 **P<.01 ****P<.0001. ANCOVA in the ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; EOT, end of treatment; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Conclusions

- In Study 501, lumateperone 42 mg + ADT showed significant improvements over placebo + ADT in depression symptom severity across 8 of 9 QIDS-SR-16 symptom domains
- Significant improvements occurred with lumateperone 42 mg + ADT in sleep disturbance, which was the most prominent symptom domain at baseline
- Lumateperone 42 mg + ADT significantly improved QIDS-SR-16 symptom domains in patients with anxious distress and across groups of baseline disease severity
- These findings support the efficacy of adjunctive lumateperone in patients with MDD with inadequate ADT response across a range of symptom domains in MDD

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Disclosures

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WR Earley and C Chen are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.

S Durgam and SG Kozauer are former employees of Intra-Cellular Therapies, a Johnson & Johnson company.

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Email questions to Willie R. Earley at wearley@its.jnj.com

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