The Histamine H4 Receptor Antagonist, JNJ 39758979, Is Effective in Reducing Histamine-Induced Pruritus in a Randomized Clinical Study in Healthy Subjects

Alexa Kollmeier, Klaus Francke, Bin Chen, Paul J. Dunford, Andrew J. Greenspan, Yichuan Xia, Xie L. Xu, Bei Zhou, and Robin L. Thurmond


Received April 21, 2014; accepted May 8, 2014

ABSTRACT

The histamine H4 receptor (H4R) is a promising target for the treatment of pruritus. A clinical study was conducted to evaluate the safety and efficacy of the H4R antagonist, JNJ 39758979 [(R)-4-(3-amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine], on histamine-induced pruritus in healthy subjects. A single oral dose of 600 mg JNJ 39758979, 10 mg cetirizine, or placebo was administered in a randomized, three-period, double-blind, crossover study. Treatment periods were separated by 22-day washout periods. A histamine challenge was administered on day 1 and at 2 and 6 hours postdose on day 1 of each treatment period. The primary efficacy endpoint was the area under the curve (AUC) of pruritus score 0–10 minutes after the histamine challenge. Secondary efficacy endpoints included wheal and flare areas assessed 10 minutes after the histamine challenge. Safety was assessed for all subjects. Of the 24 enrolled subjects, 23 individuals completed the study. One subject withdrew after completing two treatment periods. Due to a carryover effect of JNJ 39758979, only treatment period 1 was used for pruritus-related evaluations. Compared with placebo, the reduction of the AUC of pruritus score was significant for JNJ 39758979 at 2 hours (P = 0.0248) and 6 hours (P = 0.0060), and for cetirizine at 6 hours (P = 0.0417). In all treatment periods, JNJ 39758979 did not demonstrate a significant decrease in wheal or flare at either time point, although a significant reduction was achieved with cetirizine at 2 and 6 hours (P < 0.0001). Adverse eventss reported in >1 patient with JNJ 39758979 were headache (9%) and nausea (13%). In conclusion, JNJ 39758979 was effective in inhibiting histamine-induced pruritus in healthy subjects.

Introduction

Historically, the therapeutic approach to pruritus associated with skin disorders has focused on antagonism of histamine, with histamine H1 receptor (H1R) antagonists as the most widely used agents (Simons and Simons, 2011; Thurmond et al., 2014b). Efficacy of these antihistamines is predicted by the ability to block pruritus induced by application of histamine into skin. However, H1R antagonists have little, if any, effect on chronic pruritus associated with conditions such as atopic dermatitis. The control of pruritus in these diseases represents a significant unmet need for which novel, effective antipruritic therapies are required.

Emerging preclinical data suggest a role for the histamine H2 receptor (H2R) in mediating pruritic responses (Thurmond et al., 2008). In particular, it was found that scratching induced by acute application of histamine into the skin of mice could be blocked by pretreatment with an H2R antagonist and was greatly reduced in H2R-deficient mice (Dunford et al., 2007; Yamaura et al., 2009; Shin et al., 2012). Similar effects were seen in models of dermal inflammation in which both pruritus and inflammation were reduced (Cowden et al., 2010; Suwa et al., 2011; Matsushita et al., 2012; Ohsawa and Hirasawa, 2012). The combined anti-inflammatory and antipruritic activity of H2R antagonists suggests that they may provide an alternative and effective therapy for the treatment of inflammatory pruritic diseases.

JNJ 39758979 [(R)-4-(3-amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine] is a novel, potent, and selective H4R antagonist. This compound has greater than 100-fold selectivity over other histamine receptors as determined by Kᵢ (Savall et al., 2014; Thurmond et al., 2014a). In preclinical studies, JNJ 39758979 demonstrated anti-inflammatory activity in animal models of pruritus, asthma, arthritis, and dermatitis. In an animal model of pruritus in which mice received an intradermal injection of histamine, JNJ 39758979 was efficacious at reducing the bouts of scratching (Savall et al., 2014). In a double-blind, placebo-controlled, randomized, single and multiple ascending dose study to investigate the safety, tolerability, and pharmacokinetics of oral doses of JNJ 39758979 in healthy subjects, no significant safety issues
were noted and the compound demonstrated good exposure with a plasma half-life of 124–157 hours after a single oral dose (Thurmond et al., 2014a).

Given the preclinical data that suggest a role for the H4R in mediating histamine-induced pruritus and the inhibitory effect of JNJ 39758979 on scratching induced by intradermal histamine injection in mice, the effect of JNJ 39758979 on histamine-induced pruritus was studied in humans. The primary objective of this phase 1 study was to evaluate the efficacy and safety of a single 600-mg oral dose of the H4R antagonist JNJ 39758979 on histamine-induced pruritus in healthy male subjects.

Materials and Methods

Patients. Healthy male subjects aged 18–55 years were recruited for this trial (ClinicalTrials.gov identifier NCT01068223) if they had a positive response at screening (4–21 days before the first study-agent dose) to histamine challenge (i.e., one pruritus rating ≥5 using a 0–10 numeric scale within 5 minutes of a 100-μg histamine intradermal injection, measured at 1-minute intervals, and a visible flare within 5 minutes postinjection). Key exclusion criteria were any confirmed significant reactions to any drug, active skin disease, a history of atopic disease, or evidence of allergen sensitization by skin-prick testing to common aeroallergens. Anti-histamines or antidepressants with antihistamine properties were prohibited within 7 days before screening and throughout the study. Prescription and over-the-counter medications (except for paracetamol <2 g/d) and multivitamin supplements were prohibited during the study.

Study Design. In this single-center, randomized, double-blind, modified-double-dummy, placebo- and active-controlled, six-sequence, three-period crossover study, subjects were randomized to receive one of six treatment sequence groups based on a computer-generated randomization schedule prepared by the sponsor before the study. Based on this randomization code, an unblinded pharmacist or a properly trained designee, who was not associated with the study, prepared the study drug and administered the dosing. The 600 mg once-daily dose was selected for this study to provide exposures that were above the predicted efficacious concentration needed to block histamine-induced pruritus in humans based on preclinical animal models and to ensure maximal receptor occupancy appropriate for a proof-of-mechanism study with a novel agent. This study was approved by the independent Welwyn Clinical Pharmacology Ethics Committee (Hatfield, UK). All subjects provided written informed consent.

A single dose of JNJ 39758979, placebo, or cetirizine was administered on day 1 of each treatment period after subjects consumed a high-calorie, high-fat meal. Treatment periods 1 and 2 were followed by a washout period of 22 days and a follow-up visit was performed 7–10 days after treatment period 3. During each treatment period, a solution containing 100 μg histamine in 10 μl vehicle [water, 50.0% glycerin (v/v), and 0.4% penol] was injected intradermally on the right forearm before the histamine challenge/histamine prick test. A visible flare within 5 minutes postinjection was noted and the compound demonstrated good exposure with a plasma half-life of 124–157 hours after a single oral dose (Thurmond et al., 2014a).
and S.E.M. of the treatment difference as well as the 95% confidence intervals and $P$ values were estimated through the following: an analysis of covariance model with treatment, sequence, and period as fixed factors; subject nested within sequence as a random factor; and measurement of day 1 of treatment period 1 as a covariate. Similar analyses were performed for changes from day $-1$. All remaining endpoints were analyzed using similar methods as for the primary endpoints. The data for all primary and secondary endpoints are given as the mean and S.E.M.

**Results**

Between March and May 2010, 24 subjects were enrolled at a single center in Harrow, UK. Subjects were randomized to receive one of six treatment sequences of a three-period crossover treatment each comprising a single dose of placebo, 600 mg JNJ 39758979, or 10 mg cetirizine (Fig. 1). Twenty-three subjects completed the study; one subject withdrew from the study due to an AE of tooth infection and did not receive the planned treatment of treatment period 3 (JNJ 39758979). The mean participant age was 30.6 years, the mean body mass index was 24.4, and the majority of subjects were white (92%). Baseline demographics were comparable across treatment groups.

**Efficacy.** This study assessed the effect of compounds on histamine-induced skin reactions. When histamine is injected into the skin, it produces wheal along with reddening (flare) that appears almost immediately and resembles an insect bite (Sollmann and Pilcher, 1917). The edema leading to the wheal can be measured by direct observation of the area involved. The flare response is due to dilation of blood vessels leading to a red flushed area surrounding the wheal. This flare can be measured by laser Doppler imaging to determine dermal blood flow. Representative images before and after treatment with cetirizine are shown in Fig. 2. In addition to the wheal and flare response, histamine injection also causes pruritus. This was measured subjectively using a numeric 0–10 scale, with 0 indicating “no itch,” 5 indicating “intensity that incites to cool or to scratch,” and 10 indicating “unbearable itch.”

The carryover effect of JNJ 39758979 on the AUC of pruritus scores (0–10 minutes) was statistically significant at 6 hours postdose ($P = 0.0762$) but not at 2 hours ($P = 0.6358$). Similar results of a carryover effect were observed for the change from baseline in the AUC of pruritus scores (0–10 minutes). Given the statistical significance at 6 hours, pruritus-related primary and secondary efficacy endpoints were based only on data from treatment period 1 as prespecified in the study statistical analysis plan.

For all three treatment groups, at both 2 and 6 hours postdose, the mean pruritus scores peaked within the first minute and then generally decreased over 10 minutes after the histamine challenge (Fig. 3), which is consistent with the reports from literature (Bickford, 1937; Simone et al., 1987). The mean AUC of pruritus score (0–10 minutes) at baseline on day $-1$ for period 1 was similar across all three treatment groups and was $47.4 \pm 4.0$, $44.7 \pm 6.3$, and $45.3 \pm 8.3$ for the JNJ 39758979, cetirizine, and placebo groups, respectively (Fig. 4). Compared with placebo, JNJ 39758979 demonstrated a significant decrease in the primary endpoint of AUC of pruritus (0–10 minutes), with LSM score reductions of $17.429 \pm 7.1810$ ($P = 0.0248$) at 2 hours after treatment and $19.193 \pm 6.2448$ ($P = 0.0060$) at 6 hours after treatment compared with placebo (Fig. 4). The LSM for the AUC of pruritus (0–10 minutes) for the cetirizine-treated group was similar to that of the placebo-treated group at 2 hours after dosing; LSM scores were $38.450 \pm 5.0748$ and $37.833 \pm 5.0721$ for cetirizine and placebo, respectively ($P = 0.9323$). Cetirizine treatment showed a significant reduction in the AUC of pruritus at 6 hours after dosing with a LSM score reduction of $13.572 \pm 6.2376$ ($P = 0.0417$) compared with placebo (Fig. 4). Previous reports showed that cetirizine has a maximal effect on histamine-induced dermal reactions at
4–8 hours, which is consistent with that seen here (Coulie et al., 1989, 1991b; Simons et al., 1990; Lahti and Haapaniemi, 1993; Grant et al., 1999; Furue et al., 2001; Morita et al., 2005).

Compared with placebo, JNJ 39758979 demonstrated a statistically significant relief of itch at both 2 and 6 hours as measured by the major secondary endpoints of AUC of pruritus (0.5–5 minutes) \( (P = 0.0254 \text{ and } P = 0.0034, \text{ respectively}) \) and cumulative pruritus score (0.5–5 minutes) \( (P = 0.0266 \text{ and } P = 0.0034, \text{ respectively}) \) (Fig. 5). JNJ 39758979 also reduced the major secondary endpoint of maximum (worst) pruritus score, compared with placebo, with a decrease of 1.125 ± 0.6522 at 2 hours after treatment \( (P = 0.0999) \) and a statistically significant decrease of 2.125 ± 0.9343 at 6 hours \( (P = 0.0341) \) (Fig. 5). Cetirizine did not demonstrate a decrease in the AUC of pruritus (0.5–5 minutes) score \( (P = 0.8303) \) or the cumulative pruritus (0.5–5 minutes) score \( (P = 0.8776) \) at 2 hours compared with placebo (Fig. 5). Reductions were observed at 6 hours for the AUC of pruritus (0.5–5 minutes) \( (4.216 ± 3.2242, P = 0.2059) \) and the cumulative pruritus score \( (10.029 ± 7.0667, P = 0.1712) \) compared with placebo, but did not reach statistical significance (Fig. 5). For the maximum pruritus score, cetirizine showed reductions of 0.212 ± 0.6594 \( (P = 0.7511) \) and 0.764 ± 0.9448 \( (P = 0.4282) \) at 2 and 6 hours, respectively, compared with placebo (Fig. 5).

Comparisons of JNJ 39758979 with placebo at 2 and 6 hours postdose did not demonstrate a significant reduction in the major secondary endpoints of wheal or flare area (Table 1). This is in contrast with the effects of cetirizine that significantly reduced the wheal area and flare area at both 2 and 6 hours \( (P < 0.0001 \text{ for all measurements}) \) compared with placebo (Table 1).

**Post Hoc Analyses.** Post hoc analyses conducted to investigate the disparity of the carryover effect of JNJ 39758979 at 2 and 6 hours postdose indicate that the carryover effect of JNJ 39758979 could most likely be attributed to a specific interaction between JNJ 39758979 and cetirizine when they were administered in the order of JNJ 39758979 followed by cetirizine.

**Pharmacokinetics.** After treatment, JNJ 39758979 concentrations were detectable in plasma for approximately 3 weeks after a single dose in subjects who received JNJ 39758979 in periods 1 and 2 (mean of approximately 5 ng/ml) and in urine for 7 to 8 weeks after a single dose in subjects who received JNJ 39758979 in period 1 (mean of 59 ng/ml). These concentrations may be associated with the pharmacodynamic/efficacy carryover effect.

**Safety.** Of the 24 treated subjects, 8 individuals (33%) reported AEs. The most frequently reported AEs overall were headache (17%) and nausea (13%), reported by two and three subjects, respectively, who received JNJ 39758979, by zero subjects who received cetirizine, and by two and zero subjects, respectively, who received placebo (Table 2). No serious AEs or deaths occurred during the study. One subject discontinued from the study due to an AE of tooth infection of moderate intensity. The subject completed treatment periods 1 and 2 (placebo and cetirizine), but withdrew from the study before treatment period 3 (JNJ 39758979). The event was not considered related to cetirizine. There were no clinically significant changes in laboratory values, vital sign measurements, or ECG assessments.

**Discussion**

Preclinical data show a role for H4R in mediating pruritic responses. In particular, H4R antagonists blocked scratching in mice induced by intradermal injection of histamine and scratching was reduced in H4R-deficient mice (Dunford et al., 2007). Similar studies can also be performed in humans, as it was noted only a few years after the discovery of histamine that it can induce pruritus when applied to human skin (Eppinger, 1913; Sollmann and Pilcher, 1917). The fact that pruritus is a major symptom in several human diseases, coupled with the ability to carry out the same experiment in humans and mice, makes the assessment of histamine-induced pruritus an ideal
translational medicine study for testing novel therapies. This clinical study assessed the effect of the potent and selective H4R antagonist JNJ 39758979, which has no affinity for the H1R, on histamine-induced pruritus. Histamine-induced pruritus in humans is well known to be mediated by activation of the H1R, and antihistamines that target this receptor reduce the pruritus. In this study, the H1R antagonist cetirizine was used as a positive control. Cetirizine has a high affinity for the H1R (K_i 56 nM) and no affinity for the H4R (K_i 10 μM). Likewise, JNJ 39758979 is very selective for the H4R (K_i 12 nM) and has no affinity for the H1R up to a concentration of 1 μM (Table 3). The selectivity of these compounds makes them excellent choices to elucidate the contributions of the H1R and H4R. The pharmacological specificity of JNJ 39758979 for the H4R allows for unambiguous identification of a role for this receptor in mediating pruritus in humans.

JNJ 39758979 met the primary objective of this study. Compared with placebo treatment in the first period, a single dose of 600 mg JNJ 39758979 demonstrated a significant decrease in the AUC of pruritus (0–10 minutes) after histamine challenge at 2 and 6 hours after dosing in healthy subjects. JNJ 39758979 appeared to be safe when administered as a single 600-mg dose. Only 8 of the 24 treated subjects experienced AEs. The majority of these AEs were gastrointestinal, which were thought to be due to a local effect in the stomach since these effects were largely alleviated in later clinical studies by using an enteric coating that avoids dissolution in the stomach. It is unlikely that these gastrointestinal effects are a result of antagonism of the H4R; rather, these effects most likely represent unknown off-target effects or general irritation. There were no serious AEs reported. However, it should be noted that in a later clinical study (ClinicalTrials.gov identifier NCT01497119), JNJ 39758979 was found to be associated with drug-induced agranulocytosis that was thought to be related to the chemical structure and not to antagonism of the H4R.

JNJ 39758979 was not effective at inhibiting wheal and flare reactions that are also associated with intradermal histamine injection. Both of these effects were almost completely eliminated by the H1R antagonist, cetirizine, which is consistent with previous reports (Juhlin et al., 1987; Coulie et al., 1989, 1991a,b; Simons et al., 1990; Levander et al., 1991; Lahti and Haapaniemi, 1993; Grant

### Table 1

<table>
<thead>
<tr>
<th>Time Point after Dosing</th>
<th>Treatment</th>
<th>Subjects^1</th>
<th>LSM</th>
<th>S.E.</th>
<th>Difference of Active Drug versus Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LSM</td>
</tr>
<tr>
<td>Wheal area (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>Placebo</td>
<td>24</td>
<td>1.795</td>
<td>0.1139</td>
<td>-0.125</td>
</tr>
<tr>
<td></td>
<td>JNJ 39758979</td>
<td>23</td>
<td>1.919</td>
<td>0.1167</td>
<td>-0.939</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>24</td>
<td>0.856</td>
<td>0.1139</td>
<td>-0.119</td>
</tr>
<tr>
<td>6 h</td>
<td>Placebo</td>
<td>24</td>
<td>1.587</td>
<td>0.0732</td>
<td>-1.154</td>
</tr>
<tr>
<td></td>
<td>JNJ 39758979</td>
<td>23</td>
<td>1.469</td>
<td>0.0750</td>
<td>-0.119</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>24</td>
<td>0.434</td>
<td>0.0732</td>
<td>-1.154</td>
</tr>
<tr>
<td>Flare area (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>Placebo</td>
<td>24</td>
<td>52.191</td>
<td>2.1027</td>
<td>-0.936</td>
</tr>
<tr>
<td></td>
<td>JNJ 39758979</td>
<td>23</td>
<td>53.127</td>
<td>2.1400</td>
<td>-15.732</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>24</td>
<td>36.459</td>
<td>2.1027</td>
<td>-2.811</td>
</tr>
<tr>
<td>6 h</td>
<td>Placebo</td>
<td>24</td>
<td>53.691</td>
<td>2.1642</td>
<td>-0.936</td>
</tr>
<tr>
<td></td>
<td>JNJ 39758979</td>
<td>23</td>
<td>50.880</td>
<td>2.2054</td>
<td>-15.732</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>24</td>
<td>23.215</td>
<td>2.1642</td>
<td>-30.475</td>
</tr>
</tbody>
</table>

^1Number of subjects with data available in the specific treatment group.
et al., 1999; Furue et al., 2001; Morita et al., 2005). The ability of histamine to induce a wheal response is due to the expression of H1R on endothelial cells that control vascular permeability; thus, all compounds that inhibit the H1R will inhibit wheal responses. The lack of effect of JNJ 39758979 on the wheal response is proof that the compound has no activity at the H1R in humans and is consistent with the in vitro pharmacology (Savall et al., 2014). This also confirms preclinical data showing that antagonists of the H4R have no effect on histamine-induced changes in vascular permeability (Thurmond et al., 2004). A portion of the flare response may also be vasogenic and may thus account for a lack of effect of H4R antagonism; however, there is also a strong neurogenic component. Upon intradermal injection of histamine, a subset of mechanically insensitive C-fibers is activated that transmit the pruritic response to the spinal cord (Schmelz et al., 1997). The flare response is also mediated by the activation of these nerve fibers that not only transmit signals to the central nervous system, but also signal via axonal branches back to the skin leading to the release of vasodilating neuropeptides (Schmelz et al., 2000). The ability of an H4R antagonist to inhibit the pruritic response, but not the flare response, may suggest that the site of action is downstream of peripheral fiber activation, perhaps in the central nervous system. Indeed, this was previously suggested (Thurmond et al., 2008). Functional H4R expression was detected in skin-specific sensory neurons in the mouse, and direct stimulation of neurons by compound 48/80 induced scratching in mast cell–deficient mice that was inhibited by an H4R antagonist or in H4R-deficient mice (Dunford et al., 2007; Rossbach et al., 2011). This may further support that the site of action of H4R antagonism could be downstream of sensory fiber activation. However, conclusive evidence of H4R expression in the human brain and neurons is lacking, and the hypothesis that the site of action of the H4R is in the central nervous system does not explain the fact that local application of H4R agonists leads to scratching in mice (Dunford et al., 2007; Yu et al., 2010). Thus, the site of action of JNJ 39758979 for blocking pruritus is not clear and more work is necessary to elucidate the mechanisms underlying the role of the H4R in mediating pruritic signals.

One limitation of this study is that only male, mainly white, subjects were included and it is unknown as to whether the effects observed here would also be seen in female subjects or other ethnic groups. No difference in pharmacokinetics, pharmacodynamics, or safety were noted between male and female subjects in a previous phase 1 study (Thurmond et al., 2014a). An additional limitation is that a significant carryover effect for JNJ 39758979 was observed that limited the analysis of pruritus-related efficacy endpoints to data from treatment period 1 only. The carryover effect was significant at 6 hours but not at 2 hours, and only when cetirizine directly followed JNJ 39758979 in treatment sequence. Post hoc analyses conducted to investigate the disparity of the carryover effect of JNJ 39758979 at 2 and 6 hours postdose indicate that the carryover effect of JNJ 39758979 could mostly be attributed to a specific interaction between JNJ 39758979 and cetirizine when they were administered in the order of JNJ 39758979 followed by cetirizine. In light of the long half-life of JNJ 39758979 and the time of onset of action of cetirizine, it is possible that the carryover effect was related to synergistic effects of these two agents. Synergy between the H4R and H1R was noted in preclinical models of pruritus (Dunford et al., 2007; Rossbach et al., 2009; Cowden et al., 2010; Matsushita et al., 2012; Ohsawa and Hirasa, 2012). These data suggest that for both pruritus and inflammation, the combination of an H1R antagonist with an H4R antagonist may be more effective than either on its own. In the future, one could envision testing the combination of JNJ 39758979 with cetirizine, or another H1R antagonist, for additive or synergistic effects on inhibiting histamine-induced pruritus or pruritus in chronic conditions such as atopic dermatitis.

The efficacy of an H4R antagonist in the inhibition of histamine-induced pruritus in humans suggests that H4R antagonists would be effective in inhibiting pruritus known to be driven by histamine such as acute urticaria, nasal pruritus associated with allergic rhinitis, and ocular pruritus in allergic conjunctivitis. The human data presented here, in conjunction with previously published preclinical data in models of chronic pruritus, support the exploration of efficacy of H4R antagonists for the treatment of pruritus that is not well controlled by H1R antihistamines. This would include

### TABLE 3

<table>
<thead>
<tr>
<th>Selection of JNJ 39758979 and cetirizine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine Receptor</td>
</tr>
<tr>
<td>H1R</td>
</tr>
<tr>
<td>H2R</td>
</tr>
<tr>
<td>H3R</td>
</tr>
<tr>
<td>H4R</td>
</tr>
</tbody>
</table>

ªData are from Thurmond et al. (2014a).

ªData are from Levcetirizine New Drug Application 22-064 (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022064s000_PharmR.pdf), Gillard et al. (2002), and Lim et al. (2005).
pruritus associated with chronic urticaria, atopic dermatitis, and psoriasis.

Acknowledgments

The authors thank Amanda March and Jennifer Han of Janssen Services, LLC, for assistance with writing and preparing this manuscript for publication.

Authorship Contributions

Participated in research design: Kollmeier, Francke, Chen, Dunford, Greenspan, Xia, Xu, Zhou, Thurmond.

Performed data analysis: Kollmeier, Chen, Dunford, Greenspan, Xia, Xu, Zhou, Thurmond.

Wrote or contributed to the writing of the manuscript: Kollmeier, Francke, Chen, Dunford, Greenspan, Xia, Xu, Zhou, Thurmond.

References


Address correspondence to: Robin L. Thurmond, Janssen Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121. E-mail: rthurmon@its.jnj.com.