Trends in Adherence to a Revised Risk Management Program Designed to Decrease or Eliminate Isotretinoin-Exposed Pregnancies

Evaluation of the Accutane SMART Program

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Objective: To review adherence to selected procedures outlined in the System to Manage Accutane-Related Teratogenicity (SMART) program during the first year of implementation vs the procedures in effect in the year prior to initiation of the SMART program.

Design: Observational.

Setting: A novel pharmacy compliance survey and an ongoing, voluntary survey.

Patients: Female recipients of isotretinoin.

Intervention: In April 2002, Hoffmann-La Roche Inc, Nutley, NJ, manufacturer of Accutane brand isotretinoin and at that time the sole source of isotretinoin, revised earlier guidelines and instituted the SMART risk management program, which included the use of qualification stickers to affix to all prescriptions for Accutane to indicate, among other things, a negative pregnancy test just before the prescription was written. The goal of the SMART program was to decrease or eliminate isotretinoin-exposed pregnancies.

Main Outcome Measures: Use and completion of prescription qualification stickers; changes in pretherapy pregnancy testing and birth control use.

Results: The results of the pharmacy compliance survey indicated high (>90%) use of prescription qualification stickers. Results of the patient survey suggested that 9% of prescription qualification stickers within the observed user cohort were issued without a pregnancy test. Furthermore, the pregnancy rate for patients participating in the survey was similar to that reported for cohorts recruited before the SMART program.

Conclusions: The usefulness of the results derived from 2 surveys designed to evaluate the SMART program is limited by the lack of reliability and validity of the survey instruments and by questionable generalizability to all female recipients of isotretinoin. The presence of a qualification sticker may not have an impact on pregnancy testing or compliance with effective birth control behavior as outlined in the SMART program.

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SMART PROGRAM DESCRIPTION

The SMART program included several major changes to the prescribing regimen for Accutane. First, prior to writing a prescription, prescribers would read the SMART “Guide to Best Practices” provided by Hoffmann-La Roche and then sign and return a letter of understanding attesting to their knowledge of the measures to minimize fetal exposures to Accutane. In addition, Accutane prescribers were encouraged to participate in a half-day continuing medical education course developed by the manufacturer to reinforce the importance of pregnancy prevention. Prescribers were then eligible to receive Accutane qualification stickers to attach to their prescription forms. When properly completed, these stickers indicated to the pharmacist that the patient was “qualified” to receive Accutane.

For female patients, qualification involved 3 discrete steps. First, potential female recipients received education about the teratogenic effects of Accutane, signed a consent form indicating that they understood the risk associated with use of Accutane during pregnancy, and underwent an initial (screening) serum or urine pregnancy test. Second, prescribers counseled sexually active women to select and use 2 forms of effective contraception simultaneously for at least 1 month prior to initiation of Accutane therapy. The FDA analyses described herein are restricted to the DAT components of the survey, specifically the prescription compliance measures. In addition, Accutane prescribers were encouraged to participate in a half-day continuing medical education course developed by the manufacturer to reinforce the importance of pregnancy prevention. Prescribers were then eligible to receive Accutane qualification stickers to attach to their prescription forms. When properly completed, these stickers indicated to the pharmacist that the patient was “qualified” to receive Accutane.

From the date of qualification and were to be dispensed with an FDA-approved Accutane Medication Guide. Requests for refills without a new prescription and electronic, telephone, or mail prescriptions were not to be honored.

Prior to the approval of the SMART program, the FDA and Hoffmann-La Roche agreed to evaluate its effectiveness during the first year of implementation. No specific performance metrics were prespecified by the FDA. Independently, Hoffmann-La Roche proposed the following goals as primary assessment metrics: (1) to increase enrollment to 60% in a voluntary Accutane patient survey of female isotretinoin recipients at 1 year after the implementation of SMART; and (2) to demonstrate that 90% of all Accutane prescriptions are dispensed with a qualification sticker at 1 year after the implementation of SMART. To address whether the SMART program reached these objectives, Hoffmann-La Roche agreed to conduct a prescription compliance survey (PCS) in addition to ongoing surveys of Accutane use among women (eg, the Slone Survey).

PRESCRIPTION COMPLIANCE SURVEY

The PCS was a pharmacy-based instrument designed to measure compliance with qualification sticker use for Accutane prescriptions. The primary outcome of interest was compliance with qualification sticker use, defined as the presence of a qualification sticker on the prescription. Secondary outcomes were the completeness of the sticker (ie, whether it contained the required information on patient sex and qualification date), and whether the information on the sticker was correct.

The PCS was a retrospective repeated-measures survey that was designed to include 6000 randomly selected US pharmacies based on 4 strata (Table 1). The strata were weighted to obtain a representative sample of US pharmacies in each round of the PCS. Over a 2-year period, 750 pharmacies were recruited to participate each quarter from a universe of 47,046 retail US pharmacies. Pharmacies were independently selected from a national database of all pharmacies, and each pharmacy could be selected only once during the entire PCS survey period. The PCS covered only retail pharmacies; approximately 92% of all isotretinoin prescriptions are dispensed in that setting. (Of the remaining prescriptions, 4% are dispensed via mail order and 4% through other methods.)

ACCUTANE PATIENT SURVEYS

As a component of the Accutane PPP, the Slone Epidemiology Unit of Boston University implemented the Survey of Accutane Use in Women (Slone Survey) in 1989. The purpose of the survey was to “assess the compliance of physicians and patients with the Accutane PPP and to identify the rate of pregnancy during treatment with isotretinoin and during the month after treatment.” The format of the survey has remained largely unchanged since its inception and has been described in detail elsewhere. Enrollment and subsequent participation is voluntary. The survey consists of a self-administered mailed survey instrument that has 2 arms: a DAT arm (during and after treatment) and an after-treatment arm. Historically, 5000 enrollees were assigned to the DAT arm, which included 3 separate contacts with the patient at the start of, during, and after the end of a course of Accutane therapy. The FDA analyses described herein are restricted to the DAT components of the survey, specifically the responses obtained in the early phases or initiation of therapy.

The Slone Epidemiology Unit was the sole administrator of the Accutane patient survey from inception through September 2002. Beginning in October 2002, the Degge Group Ltd, Arlington, Va, in cooperation with SI International, McLean, Va (Degge/SI), became the prime patient survey administrator.
for Accutane isotretinoin. At this time, Degge/SI also introduced an updated questionnaire, which included new questions specifically designed to measure compliance with novel features of SMART in comparison with the PPP, specifically information on the presence of a prescription qualification sticker.

Analysis of patient survey data was conducted using an anonymized data set from Degge/SI and periodic reports provided by the Slone Epidemiology Unit. Analyses of the Degge/SI data set were conducted using SAS software, version 8.11 (SAS Institute, Cary, NC). The data set comprised responses from 5489 women who received the questionnaires between October 2002 and April 1, 2003. The overall DAT response rate (the proportion of enrolled women who returned the questionnaire) was 83%. Twenty respondents reported no plans to start Accutane therapy and were excluded from all FDA analyses. Of the remaining 5469 respondents, 80.9% completed the questionnaire within 30 days of enrollment. Twelve percent responded later than 30 days, and 7.1% had an invalid or missing date. A total of 1192 (22%) reported that they had undergone a previous course of Accutane. Among 4596 participants aged 15 to 45 years who did not indicate that they had undergone menopause or a hysterectomy and who provided a response for sexual activity status, 1806 (39.3%) reported sexual activity since starting the current course of Accutane therapy.

Trends in pregnancy testing within the Slone Survey population (per calendar quarter) in the year prior to initiation of the SMART program through the first year of the SMART program were provided by aggregation of reports as provided by the Slone Survey. For the purposes of this analysis, the absolute enrollment rate was defined as the proportion of women who enrolled in either the Slone Survey or the Degge/SI survey per calendar quarter divided by an estimate of the number of unique women using Accutane per calendar quarter. Estimates of the number of unique women using Accutane per calendar quarter were obtained by dividing the total number of prescriptions for women in each quarter by the average number of prescriptions per woman per treatment course for the year prior to and in the first year of the SMART program. This model assumed an average of 3.7 prescriptions per treatment course per unique woman as was observed within a large cohort of Accutane recipients.

A pregnancy rate was calculated for participants in the Degge/SI survey. The numerator for this rate was based on a positive (“Yes”) response to either question 37 from the initiating therapy instrument or question 17 from the during therapy instrument (“Have you been pregnant at any time since you first started taking Accutane?”). Because a woman undergoing a repeated course of therapy (about 22% of the total cohort) may correctly answer this question as “Yes” based on an unexposed pregnancy in between treatment courses, a pregnancy rate calculation was restricted to women receiving their first course of therapy (n=4277).

Since these data, including the results of the PCS and the Accutane Patient Survey, were designed to be descriptive and are limited by both survey design and generalizability, no statistical tests were conducted.

### RESULTS

**PARTICIPATION IN PCS**

The response from recruited pharmacies for the first 5 rounds of the PCS is detailed in Table 2. The first survey had a response rate of approximately 25%. Subsequent survey response rates were between 50% and 60%. Although the percentage of responding stores remained steady, the number of Accutane prescriptions captured shows a consistent downward pattern, starting with a high of 319 prescriptions for the first survey round and decreasing to 181 prescriptions by the fifth survey round.

**PCS RESULTS**

Overall, the results were consistent across sex, payer type, and age. There were some differences in the pharmacy strata, specifically for prescription volume and population density. In the June 2002 survey, pharmacies with a volume of 2500 to 4999 prescriptions per month were more likely to receive Accutane prescriptions with incomplete stickers (missing sex and/or prescription date) than pharmacies with either a higher or lower prescription volume (89% complete for 2500–4999–prescription stores vs 100% and 97% complete for 1–2499– and ≥5000–prescription stores, respectively). Compliance and completeness across all survey waves were generally greater than 90%. When the results were stratified by rural vs urban stores, rural pharmacies were more likely than urban stores to receive an Accutane prescription without a sticker (Table 3), although this difference appeared to decrease over time.

**PATIENT SURVEY ENROLLMENT**

As part of the changes instituted with the SMART program, 80% of enrollees were assigned to the DAT survey and 20% to the after-treatment instrument. The number and percentage of women who enrolled in an Accutane patient survey for the year prior to the start of SMART and in the first year of the program are listed in Table 4 and illustrated in Figure 1. The quarterly enrollment rate for the year prior to the start of SMART ranged from 15% to 18%. In the first year of SMART, the quarterly enrollment rate ranged from 21% to 26%.
The qualification sticker is designed to document that the patient received education and counseling on pregnancy prevention. The relationship between qualification sticker and any birth control use among fertile and sexually active 15- to 45-year-old Degge/SI participants is detailed in Table 7. As in Table 6, there does not appear to be a strong relationship between the presence of a qualification sticker and patient compliance with Accutane contraceptive guidelines. Birth control use was high among respondents reporting current sexual activity regardless of qualification sticker presence. Table 7 also reflects that a small fraction (3%) of these women within the subset of participants with information on birth control and qualification sticker deny use of any form of birth control.

FDA ANALYSES OF PARTICIPANTS IN THE DEGGE/SI SURVEY

Selected attributes of patients participating in the Degge/SI survey are outlined in Table 5. Eighty percent of participants reported signing a consent form, 9% reported signing no consent form, and 11% were uncertain or did not answer the question. Most participants (81%) reported receipt of a medication guide, although a large fraction (15%) were uncertain or did not answer the question. In a finding consistent with the PCS, more than 90% of the patients reported a qualification sticker on their Accutane prescription, 2.5% of participants reported no sticker, and 5.5% did not know or did not answer the question. Among Degge/SI participants 15 to 45 years old who had not reported a hysterectomy, menopause, or infertility, 91% reported at least 1 pregnancy test, and 66% reported 2 tests prior to initiation of treatment with Accutane. Reports of pregnancy testing among the subset of sexually active participants were slightly higher, at 92% and 68%, respectively. In addition, most (96%) of these sexually active participants reported use of some form of birth control, with 83% reporting use of a primary method. However, only 46% of these participants reported use of appropriate birth control (as described in the Accutane label) consisting of 1 primary method and 1 secondary method. As noted herein, a small percentage (about 4%) of sexually active and apparently fertile women aged 15 to 45 years within the Degge/SI survey denied use of any form of birth control.

BIVARIATE ANALYSES

Further analysis shows that the introduction of qualification stickers to the isotretinoin-dispensing process may not have had any impact on its main purpose (ie, improvement of pregnancy testing). Table 6 outlines the relationship between qualification sticker and pregnancy testing among selected participants in the Degge/SI cohort. The presence of the qualification sticker did not appear to relate to performance of a pregnancy test: testing was high with (91%) and without (90%) a qualification sticker. Of particular interest, 9% of issued qualification stickers were, by patient report, not linked to a pregnancy test (Table 6).

TRENDS IN ANY PREGNANCY TESTING BEFORE AND AFTER IMPLEMENTATION OF THE SMART PROGRAM WITHIN THE SLONE SURVEY

Data reported by the Slone Epidemiology Unit and submitted to the FDA suggest that the rate of any pregnancy testing prior to initiation of therapy with isotretinoin increased from a range of 77% to 85% in the year prior to initiation of the SMART program to 91% to 92% in the first year of the SMART program. These data are shown in Figure 2, which depicts that the improvement, at least within the cohort observed by the Slone Epidemiology Group, began to take place shortly before implementation of the SMART program and appears to have plateaued thereafter.

PREGNANCIES WITHIN THE DEGGE/SI COHORT

The FDA examined the Degge/SI cohort for reports of pregnancy for calculation of an Accutane-exposed pregnancy rate. The Degge/SI data set contains 15 reports of pregnancy among the 4277 women on their first course of therapy. At the time of the survey, the median age of these 15 women was 22 years (mean, 24.5 years) with a range of 16 to 39 years. This is similar to the median (22 years) and mean (24.4 years) of the total cohort of first-time users. Eight women reported pregnancy on the “initiating” instrument and 7 on the “during therapy” instrument. Based on the report of 15 pregnancies, the crude observed pregnancy rate for first-course users within the Degge/SI cohort was 15/4277, or 3.5/1000. The denominator used in this calculation (4277) included some women who had not completed treatment at the time of reporting and who might therefore report an Accutane-exposed pregnancy during further follow-up. Thus, as this rate is censored, it likely represents an underestimate of the rate to be realized when all these participants complete follow-up, as described by Mitchell et al.7

The SMART program introduced a qualification sticker to be applied to each prescription. The purpose of this sticker was to document that the patient was not preg-
Table 4. FDA Quarter-Yearly Estimates of Trends in Participation in Accutane Patient Survey Before and After SMART Initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Last 4 Quarters Before SMART</th>
<th>First 4 Quarters of SMART</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of survey enrollees*</td>
<td>7903</td>
<td>7897</td>
</tr>
<tr>
<td>Dispensed Rx volume for quarter†</td>
<td>377 000</td>
<td>338 000</td>
</tr>
<tr>
<td>Rx volume to female recipients‡</td>
<td>188 500</td>
<td>169 000</td>
</tr>
<tr>
<td>Percentage of total female utilization§</td>
<td>14.1</td>
<td>12.7</td>
</tr>
<tr>
<td>Estimate of total unique female recipients</td>
<td>50 900</td>
<td>45 700</td>
</tr>
<tr>
<td>Enrollment rate, %</td>
<td>15.5</td>
<td>17.3</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; Q, quarter; Rx, prescription; SMART, System to Manage Accutane-Related Teratogenicity.

*Data from Hoffmann-La Roche.⁵
†Data from IMS Health.¹⁰
‡Based on assessment of 1:1 male-female Rx distribution; FDA custom calculations were based on IMS Health data.¹⁰
§Based on division by female Rx volume of quarter by total Rx volume to female recipients (1 334 000); FDA custom calculations were based on IMS Health data.¹⁰
‖Based on multiplication by percentage of total female utilization of quarter by 360 500; unique female count of 360 500 based on an average of 3.7 Rxs per patient; FDA custom calculations were based on IMS Health data.¹⁰

Table 5. Univariate Analysis of Selected Attributes Collected From Patients Participating in Degge/SI Isotretinoin Survey*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent forms</td>
<td>80.0</td>
</tr>
<tr>
<td>Signed a consent form</td>
<td>81.0</td>
</tr>
<tr>
<td>Signed no consent form</td>
<td>9.3</td>
</tr>
<tr>
<td>Uncertain or not answered</td>
<td>10.7</td>
</tr>
<tr>
<td>Received medication guide</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81.0</td>
</tr>
<tr>
<td>No</td>
<td>4.0</td>
</tr>
<tr>
<td>Uncertain or not answered</td>
<td>15.0</td>
</tr>
<tr>
<td>Prescription carried qualification sticker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92.1</td>
</tr>
<tr>
<td>No</td>
<td>2.3</td>
</tr>
<tr>
<td>Someone else picked up prescription or uncertain or not answered</td>
<td>5.6</td>
</tr>
<tr>
<td>Pregnancy testing prior to initiation of therapy†</td>
<td></td>
</tr>
<tr>
<td>Report of at least 1 pregnancy test</td>
<td>90.8</td>
</tr>
<tr>
<td>Report of ≥2 pregnancy tests</td>
<td>66.0</td>
</tr>
<tr>
<td>Birth control among the sexually active†</td>
<td></td>
</tr>
<tr>
<td>Any form of birth control§</td>
<td>96.8</td>
</tr>
<tr>
<td>Any primary form of birth control</td>
<td>83.0</td>
</tr>
<tr>
<td>Appropriate birth control‖</td>
<td>46.4</td>
</tr>
</tbody>
</table>

Abbreviation: Degge/SI, the Degge Group Ltd (Arlington, Va) and SI International (McLean, Va).

*N = 5469 unless otherwise noted.
†Restricted to 4598 fertile women aged 15 to 45 years who provided information on pregnancy testing who reported starting isotretinoin therapy.
‡Restricted to 1841 fertile women aged 15 to 45 years who engaged in or anticipated sexual activity during treatment with isotretinoin who reported starting isotretinoin therapy.
§Primary birth control is defined in approved labeling as oral contraception, tubal ligation, injectable, implantable, insertable, or patch contraceptives, vasectomy, or intrauterine device.
‖Appropriate, per approved labeling, requires 2 forms of birth control, one of which must be a "primary" method.

Figure 1. Food and Drug Administration model showing trends in enrollment in isotretinoin patient survey from the 4 quarters before initiation of the revised risk-management program (indicated by the arrow) and the following 4 quarters.

nant at the time of prescribing and that she received education and counseling on pregnancy prevention. Hoffman-La Roche and the FDA agreed to a new and specialized PCS to measure compliance with qualification stickers. Based on the survey results, compliance with qualification stickers appears to be quite high.

However, aspects of the survey implementation and response rate make it unclear if the survey is truly representative of the national picture or if it can achieve the stated objective of measuring sticker compliance. Two major limitations of the overall PCS are the low pharmacy response rate and the low number of prescriptions captured for analysis. The most successful survey wave yielded a response rate of only 60%. This response rate is lower than typically obtained in surveys that combine mail and telephone methods. When the response rate is examined by the predetermined strata, a consistent picture emerges. Large, urban stores are consistently underrepresented, as are high-volume pharmacies. In the third wave of the study, 4 pharmacy chains (Walgreens, CVS, Eckerd, and Rite Aid) and 1 retailer (Wal-Mart) were removed from the list of pharmacies that could be recruited. Because these stores are among the largest pharmacy chains and pharmacy retailers in the United States, their exclusion increased the likelihood that the sample would not be generalizable to the population at large.

The patient survey used after the SMART program began was similar to that used before the program, but it contained additional questions relating to SMART program components. However, both the Slone and the Degge/SI survey instruments had significant limitations of which must be a "primary" method.
Table 6. Relationship Between Qualification Sticker and Pregnancy Testing for All Apparently Fertile Enrollees Aged 15 to 45 Years*

<table>
<thead>
<tr>
<th>Pregnancy Test</th>
<th>Qualification Sticker</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3908 (91)</td>
<td>3988</td>
</tr>
<tr>
<td>No</td>
<td>332 (9)</td>
<td>402</td>
</tr>
<tr>
<td>Total</td>
<td>4300</td>
<td>4400†</td>
</tr>
</tbody>
</table>

*Excludes postmenopausal women and those reporting hysterectomy. Pregnancy testing included any pregnancy testing performed at a physician's office or performed at home but reported to the physician and is restricted to women who reported starting isotretinoin therapy. Except for totals, data are reported as number (percentage) of isotretinoin recipients.
†Excludes 319 records with missing data for either qualification sticker or pregnancy test.

Table 7. Relationship Between Qualification Sticker and Any Birth Control Use for Sexually Active, Apparently Fertile Enrollees Aged 15 to 45 Years*

<table>
<thead>
<tr>
<th>Any Birth Control Use</th>
<th>Qualification Sticker</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1671 (97)</td>
<td>1741</td>
</tr>
<tr>
<td>No</td>
<td>44 (3)</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>1715</td>
<td>1788†</td>
</tr>
</tbody>
</table>

*Excludes postmenopausal women and those reporting hysterectomy. Women were considered to use any birth control if they reported current use of any birth control method or tubal ligation or vasectomy in partner. Any birth control use, as shown in this analysis, is probably an overestimate because women who reported vasectomy in their partner were included in the any birth control category whether or not they indicated also using a second birth control method, as required per approved labeling. This analysis approach was necessary because of the poor structure of the questionnaire with regard to birth control using tubal ligation and vasectomy leading to potential for confusion. In addition, vasectomy may not pertain to all potential partners. The cohort is restricted to women who reported starting isotretinoin therapy. Except for totals, data are reported as number (percentage) of isotretinoin recipients.
†Excludes 54 records with missing data for qualification sticker.

...tions, including sensitive (and potentially embarrassing) questions, questions about past events (which may introduce recall bias), possibly excessive survey length, and complex survey skip pattern(s). (Detailed information on the survey instrument is contained in the FDA review.) These limitations may have reduced response accuracy and raise questions about the validity and reliability of the data. In addition, the survey is hampered by a voluntary design and low enrollment rate. Although low enrollment rate is not necessarily indicative of systematic bias, it can be an indicator of a problem of a lack of generalizability or representativeness of the survey results. This is particularly important in the case of voluntary surveys.

However interesting and potentially problematic specific results pertaining to reported patient behaviors may be, the determination of a pregnancy rate following new labeling could be argued as the final arbiter of success of the labeling. In a presentation before the FDA Dermatologic Drugs Advisory Committee Meeting (Gaithersburg, Md) on September 18, 2000, Mitchell et al reported 992 pregnancies among 339,994 women completing follow-up in the Slone Survey (through 1999), for an absolute incidence rate of 2.9 per 1000 women. The observed pregnancy rate for the initial Degge/SI was similar (3.5/1000). Thus, these data suggest that the efforts implemented in the new labeling did little to affect the absolute pregnancy rate within the population included in the Degge/SI patient survey, which began enrollment fully 6 months after the initiation of the SMART program. Data shown in Figures 1 and 2 suggest that clinicians were changing selected practices well before initiation of the SMART program.

In sum, while the PCS and patient surveys had limitations, they provide the best data presently available to evaluate adherence to the SMART program by prescribers, pharmacists, and patients. Although these data do not support confidence in the generalizability of the results from the patient survey to the broader population of isotretinoin recipients, they do provide us with some insights into the behaviors of some patients taking Accutane. There was some improvement in enrollment into the voluntary patient surveys and in certain behaviors following initiation of the SMART program, which incorporated changes to approved isotretinoin labeling. Most interesting, in our opinion, is the study of the qualification sticker, both as a novel risk management tool and as a surrogate for adherence to the new isotretinoin labeling. Self-reported utilization of the qualification stickers in the first year following introduction appears quite high, which suggests that stickers were accepted by the practicing community. However, bivariate analyses suggest that the presence of a qualification sticker may not impact performance of pregnancy testing or compliance with birth control use.

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Disclaimer: The views expressed herein are those of the authors and do not necessarily represent those of the FDA or imply its endorsement.

Previous Presentation: Some of these data and analyses, specifically those found in references 6 and 14, were
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REFERENCES


