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# Guidance for Industry

## Acne Vulgaris: Developing Drugs for Treatment

### *DRAFT GUIDANCE*

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For questions regarding this draft document contact (CDER) Frank Cross at 301-827-2020.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**September 2005  
Clinical/Medical**

# Guidance for Industry

## Acne Vulgaris: Developing Drugs for Treatment

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*Office of Training and Communications  
Division of Drug Information, HFD-240  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573  
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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

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**Guidance for Industry<sup>1</sup>**  
**Acne Vulgaris: Developing**  
**Drugs for Treatment**

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This document is intended to provide guidance to the pharmaceutical industry on the development of drug products for the treatment of acne vulgaris other than nodulocystic acne. The information presented will help applicants plan clinical studies, design clinical protocols, implement and appropriately monitor the conduct of clinical trials, collect relevant data for analysis, and perform appropriate types of analyses of study data.

This guidance does not address systemic retinoid therapies, which may not have appropriate risk-benefit profiles for non-nodulocystic acne therapy. Development programs for these treatments should be discussed with the review division before initiation.

The recommendations in this guidance are based on careful assessment of important issues raised in the review of clinical trials for acne vulgaris. Applicants are encouraged to discuss development plans with the review division before embarking on studies to ensure that the clinical trial design and analysis plan meet defined objectives. The FDA’s

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<sup>1</sup> This guidance has been prepared by the Division of Dermatologic and Dental Drug Products in the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

**Paperwork Reduction Act of 1995:** This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collection of information in this guidance has been approved under OMB Control Number 0910-0001.

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36 guidance for industry *Format and Content of the Clinical and Statistical Sections of an*  
37 *Application*<sup>2</sup> and ICH E9<sup>3</sup> contain additional information.

38  
39 FDA's guidance documents, including this guidance, do not establish legally enforceable  
40 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and  
41 should be viewed only as recommendations, unless specific regulatory or statutory  
42 requirements are cited. The use of the word *should* in Agency guidances means that  
43 something is suggested or recommended, but not required.

44

45

## **II. CLINICAL BACKGROUND**

46

47  
48 Acne vulgaris is a chronic disease of sebaceous follicles that is multifactorial in etiology  
49 and varies in severity as evidenced by lesion type, size, numbers, scarring, and post-  
50 inflammatory pigmentary changes. The severity of acne vulgaris (i.e., amount of  
51 inflammation and number of lesions) can wax and wane in a given patient. A variety of  
52 drug products, topical and systemic, are currently available to treat acne. Acne occurs  
53 more frequently on the face, but can also occur on nonfacial skin (e.g., back, shoulders,  
54 chest).

55

### **A. Lesion Types**

56

57  
58 There are two major types of acne lesions: noninflammatory and inflammatory.  
59 Although most drug products for acne are intended for the broad indication of acne  
60 vulgaris, some products have been developed that only target one of these two specific  
61 subsets of acne vulgaris lesions.

62

63 Noninflammatory lesions of acne are the open (blackheads) or closed (whiteheads)  
64 comedones. Closed comedones may be more difficult to detect visually and may require  
65 stretching of the skin to aid in visualization. These lesions, especially closed comedones,  
66 may be precursors to the larger inflammatory lesions and therefore are of clinical  
67 importance.

68

69 Inflammatory lesions are divided into papules, pustules, and nodules/nodulocystic  
70 lesions, depending on the severity and location of the inflammation within the dermis.  
71 The papules and pustules have surrounding halos of erythema allowing for their  
72 characterization as inflammatory. Nodules are typically erythematous and often tender  
73 and/or painful. Additionally, they are deep-seated in the skin (i.e., centered in the dermis  
74 or subcutis). Nodules have been defined as being greater than 5 mm in diameter. The  
75 borders of these lesions may be difficult to determine because of the associated  
76 erythema/inflammation.

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<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

<sup>3</sup> See ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (<http://www.fda.gov/cder/guidance/index.htm>)

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**B. Overall Acne Severity**

There is no single uniform, standardized, and reproducible grading system for severity of acne. Acne severity is dependent on the numbers and types of lesions present and the extent of involvement (i.e., the body areas affected). (See Section III.A.2., Baseline Lesion Counts.)

A number of acne grading systems have been described, some with inherent difficulties with regard to use. Such difficulties include inadequately defined grades of severity or excessively small differences between grades to be objectively evaluated. An Investigator’s Global Assessment (IGA) scale that may be useful for assessing overall acne severity is described in Section IV.A.1.

**C. Patient Population**

Acne vulgaris is primarily a disease beginning with and extending beyond puberty, but can persist past the third decade of life. Although acne vulgaris affects both genders, severity may be greater in male patients. Acne vulgaris occurs in all races and across the United States.

**III. DRUG DEVELOPMENT PLAN**

**A. Clinical Considerations**

*1. General*

The Agency recommends that phase 2 clinical studies provide sufficient information to optimize dose and duration of treatment chosen for phase 3 evaluation (with adequate consideration given to both safety and efficacy before end-of-phase 2 discussion). In general, a minimum treatment duration of 12 weeks is needed to demonstrate efficacy. We recommend considering a post-treatment follow-up period to evaluate recurrences following treatment discontinuation.

It is important that all drug products for acne be evaluated for safety and efficacy in the treatment of facial acne. Applicants are encouraged to demonstrate the safety and efficacy of the investigational drug in at least two adequate and well-controlled studies. We recommend that these trials be randomized, blinded, multicenter trials with suitable comparator arms, which usually include a vehicle or placebo control. Additional assessments for safety and efficacy in the treatment of nonfacial acne can be included for topical products and should be included for all systemic acne medications.

Patients are often recruited for study entry at their worst severity and usually improve during the course of therapy, whether the therapy is active or placebo (vehicle in the case

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122 of topical drugs). A demonstration of superiority against a placebo arm is generally  
123 needed for clinical studies.

124

125 We recommend that applicants enroll a population that is representative of the age, race,  
126 gender, and geographic location of acne patients in the United States. (See also ICH  
127 guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data*  
128 and guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials*.)

129

### 130 2. *Baseline Lesion Counts*

131

132 Baseline acne severity is a key element of the enrollment criteria. Baseline lesion counts  
133 are expected to have a major influence on efficacy outcomes in acne trials. Since change  
134 in lesion counts from baseline may not always translate into a successful IGA outcome, it  
135 is recommended that power calculations be based on both endpoints (see Section IV.,  
136 Study Design). As the range of baseline lesion counts is expected to affect the success  
137 rates of the outcomes, and may vary from drug to drug, applicants are encouraged to  
138 investigate the optimal range of baseline lesion counts to demonstrate success before  
139 initiation of phase 3 studies.

140

141 The baseline score of the IGA severity scale should be consistent with the baseline lesion  
142 counts. However, no numerical range of lesions for categorizing the IGA is  
143 recommended. This is because the IGA is the investigator's or physician's overall  
144 general assessment of the patient's condition and is considered to be more subjective than  
145 the purely numerical lesion count. It also takes into account the quality, as well as the  
146 quantity, of the acne lesions.

147

### 148 3. *Targeted Acne Therapy*

149

150 If a drug product is developed specifically for either inflammatory lesions or  
151 noninflammatory lesions of acne, labeling should reflect the specific type of lesion  
152 studied with reference to lack of proven efficacy for the lesion type not studied.

153

154 For drugs specifically intended to treat either inflammatory or noninflammatory lesions,  
155 it is appropriate for both lesion counts and the IGA to be assessed. Superiority will need  
156 to be demonstrated for both the targeted lesion type and the IGA. We recommend that  
157 the IGA allow for a clinical and statistical evaluation of the investigator's overall  
158 qualitative assessment of the acne severity in each patient. However, emphasis in the  
159 IGA regarding the lesion type not being targeted may be modified. To show that there is  
160 no worsening of the nontargeted lesion type, we recommend the endpoint for the  
161 nontarget lesion count demonstrate noninferiority of the active treatment to the vehicle at  
162 the prespecified time point. It is important that an appropriate noninferiority margin be  
163 selected to maintain a substantial proportion of the expected improvement from baseline  
164 for the nontargeted lesions in the vehicle or placebo treatment group.

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166 At the end of phase 2 and before initiation of phase 3 trials, we recommend that the  
167 applicant specify if a drug product would be indicated for only inflammatory, only  
168 noninflammatory, or both types of lesions of acne.

169  
170 If the drug product under development is expected to be used together with another  
171 marketed drug therapy for acne, it is important that the clinical study design reflect such  
172 co-use or adjuvant use. We recommend consultation with the Agency before the conduct  
173 of these types of trials.

174  
175 As there are specific informational needs with regard to many treatments for nodular  
176 acne, it is recommended that applicants seek additional guidance from the Agency  
177 regarding treatments targeted for nodular/nodulocystic acne.

178  
179 *4. Fixed Combination Drug Products for Acne Vulgaris*

180  
181 Fixed combination topical products for the treatment of acne vulgaris are considered  
182 under 21 CFR 300.50 and require evidence for the contribution of each active component  
183 that is claimed to provide for additional safety or efficacy. In study design, we  
184 recommend consideration be given to active components that may target a specific lesion  
185 type.

186  
187 Although evidence for efficacy may rely on comparison with a reference-listed  
188 combination drug product, comparison of only test and reference-listed combination drug  
189 product may be insufficient. The contribution to efficacy of different active ingredients  
190 may vary among different vehicles. Because of the complexity of clinical trial design, we  
191 recommend applicants seek further guidance from the Agency before the conduct of  
192 studies for fixed combination drug products.

193  
194 *5. Safety Considerations*

195  
196 For topical drug products, dermal safety studies with the final to-be-marketed drug  
197 product are recommended. It is important for these trials to provide information  
198 regarding cumulative irritancy (at least 30 evaluable subjects), contact sensitization (at  
199 least 200 evaluable subjects), phototoxic (at least 30 evaluable subjects), and  
200 photocontact allergic potential (at least 50 evaluable subjects). These trials are usually  
201 conducted simultaneously with phase 3 clinical trials, although preliminary dermal safety  
202 evaluations could be conducted during development of the to-be-marketed formulation.

203  
204 Dermal provocative irritation studies may be waived if phase 2 safety data demonstrate  
205 that the product is irritating and the Agency determines that this information is adequate  
206 for labeling purposes. Dermal irritation and sensitization (allergenicity) studies can be  
207 combined as long as a sufficient number of subjects are included for sensitization  
208 evaluation. Phototoxicity and photosensitization studies may be waived if there is no  
209 absorption of the drug product by UVB, UVA, or visible light (280 to 700 nm).

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211 Safety assessments, for short-term use, of both oral and topical acne drug products can  
212 include routine chemistry and hematology profiles. Other safety parameters may be  
213 appropriate depending upon any safety signals found in preclinical studies.  
214

215 Given the natural history of acne vulgaris, acne drug products have the potential for  
216 chronic use. Therefore, we recommend addressing long-term safety. Applicants are  
217 referred to the ICH E1A guidance<sup>4</sup> for assistance in determining the number of subjects  
218 exposed and duration of treatment needed to provide an acceptable safety database.  
219

### **B. Biopharmaceutical Considerations**

220  
221  
222 Pharmacokinetic studies to assess the degree of and/or potential for systemic absorption  
223 may be needed to fulfill the requirements of 21 CFR part 320 (Bioavailability and  
224 Bioequivalence Requirements). Under this section, a new drug application (NDA) must  
225 either contain an assessment of in vivo bioavailability or sufficient information which  
226 would allow the Agency to issue a waiver of in vivo bioavailability testing. In general,  
227 waivers of in vivo biostudies are the exception and are only granted in specific cases.  
228 Because of the variable dosing nature of topical products, we recommend that studies of  
229 the in vivo assessment of systemic exposure be done under so-called *maximal use*  
230 *conditions*. The recommended elements of such a maximal use study are as follows:  
231

- 232 1) A formulation identical to the clinically studied/to-be-marketed formulation  
233 should be used.  
234
- 235 2) The study should be done in an adequate number of patients with area of  
236 involvement and disease severity index/measuring toward the upper end of that in  
237 the proposed indication to include at least the face, shoulders, chest, and back.  
238
- 239 3) The topical dosing used should represent the maximal dosing anticipated in both  
240 phase 3 trials and in the proposed package insert for the following:  
241
  - 242 a) Frequency of dosing
  - 243 b) Duration of treatment
  - 244 c) Use of highest proposed strength
  - 245 d) Extent of involved area to be treated at one time
  - 246 e) Amount applied per square centimeter
  - 247 f) Method of application/site preparation  
248
- 249 4) The analytical method should be properly validated for both parent compound and  
250 metabolites.  
251

252 The objective of this study is to maximize those elements affecting dermal penetration  
253 such that systemic absorption can be determined. We recommend, when possible, that

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<sup>4</sup> See ICH guideline for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (<http://www.fda.gov/cder/guidance/index.htm>)

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254 the resulting pharmacokinetic data be analyzed using standard pharmacokinetic metrics  
255 (AUC,  $C_{max}$ ,  $T_{max}$ ). It is also recommended that the study protocols incorporate  
256 evaluations for cutaneous safety.

257

258

259 **IV. STUDY DESIGN**

260

261 The Agency recommends that the study protocol for evaluation of acne vulgaris clearly  
262 specify the objectives of the trial, the patient population, study drug dosage and duration  
263 of treatment, primary endpoints, and key planned analyses. In addition, we recommend  
264 the study design support the proposed claims by taking into consideration the following  
265 factors:

266

267 1) **Sample size:** It is important that the sample size be sufficiently large to support  
268 the overall safety and efficacy claims. We recommend the study be powered to  
269 ensure at least 80 percent power with a 2-sided Type I error rate of 0.05. It is  
270 important that the protocol provide details concerning sample size calculations for  
271 each of the co-primary endpoints: changes from baseline in inflammatory and  
272 noninflammatory lesion counts and success according to the IGA. We also  
273 recommend the study be adequately powered for all co-primary endpoints. For  
274 each of these co-primary endpoints, it is important that the protocol specify  
275 estimated treatment effect for each comparator. For noninferiority trials, it is also  
276 important for the noninferiority margin to be prespecified and discussed with the  
277 Agency. Unequal treatment allocation of patients to the various treatment arms  
278 might help keep the sample size manageable. Such unequal treatment allocation  
279 can be particularly useful for evaluation of combination drug products (see  
280 Section III, Drug Development Plan).

281

282 2) **Randomization and stratification:** Randomization is intended to allocate  
283 patients to treatment groups to reduce bias and to ensure that the statistical  
284 procedures can be appropriately applied. As baseline lesion counts are expected  
285 to have a significant effect on outcomes, it is important to make a considerable  
286 effort to ensure random allocation of subjects to treatment arms to reduce bias.  
287 Although randomization is intended to balance treatment allocation for  
288 confounding factors, there is always a chance that randomization may fail to  
289 achieve balance, particularly in smaller trials.

290

291 If there are known factors that are expected to have a large influence on outcome,  
292 stratification can be used to balance patient assignments for these factors instead  
293 of relying solely on simple randomization. However, we recommend that  
294 stratification be limited to the most influential factors to avoid having a large  
295 number of strata and consequently a small number of subjects per cell. Because  
296 stratification implies constraints on randomization, the statistical analysis for  
297 studies that have been stratified for certain factors should account for these  
298 factors. Since some degree of variation in efficacy across patients of different

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299 sites or geographic areas is expected, we recommend randomization by study site  
300 to balance the treatment arms in acne trials.

301

302 3) **Blinding:** Because efficacy assessments of acne, in particular the IGA, have a  
303 high degree of subjectivity, it is important that the highest degree of patient and  
304 assessor blinding be sought to achieve credible inference. Blinding may be  
305 compromised if there is a marked difference in the adverse event profile between  
306 the comparators. Every effort should be taken to preserve blinding, such as using  
307 an independent assessor (a qualified independent clinical assessor would provide  
308 the scoring of record for those aspects of clinical assessment to be blinded).

309

### 310 **A. Primary Endpoints**

311

312 Many methods exist for assessing the severity of acne and almost all of them use an  
313 ordinal scale for assessing global severity (Lehmann et al. 2002). The primary difficulty  
314 in developing a standardized ordinal scale is the pleomorphic nature of acne, as is  
315 pertinent to the mixture of lesion types, sites of involvement, the variable characteristics  
316 of the lesions (especially the inflammatory types), and the variability in the progression  
317 of acne lesions. However, this inherent difficulty provides the basis for the categorical  
318 utility of having such a global assessment (Allen 1980; Feinsein 1977; Plewig et al.  
319 1992).

320

321 Use of lesion count assessments alone as an endpoint may be less than reliable because of  
322 the lack of appreciation for the variable expression of acne vulgaris with a strictly  
323 quantitative definition (e.g., size of lesions, intensity of inflammation, and location of  
324 lesions). Although reduction in lesion counts may indicate improvement of acne severity,  
325 clinical perception of a given lesion count reduction (e.g., 50 lesions less) is different for  
326 various baseline lesion counts (e.g., 100 versus 53 lesions). In addition, precision  
327 achieved with lesion counts can be difficult and can vary even among clinicians who are  
328 experienced in counting lesions of acne vulgaris. Variability of lesion counts among  
329 raters has been shown to increase as the number of acne lesions on a patient increase  
330 (Lucky et al. 1996). Finally, although individual lesion counts have often been employed  
331 successfully in the investigational setting, their practicality and value for use in the  
332 clinical setting have been questioned (Pochi et al. 1991).

333

334 Combining the two approaches of ordinal global assessment scale and lesion count  
335 assessments allows for a balanced approach toward the evaluation of acne severity. The  
336 Agency continues to evaluate new metrics and alternative methods as they are developed  
337 for evaluating acne severity.

338

339 We recommend for clinical studies investigating the effect of a therapy on acne severity,  
340 co-primary endpoints that evaluate an IGA, and acne lesion counts.

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1. *Investigator’s Global Assessment*

The Agency recommends that the IGA be a static evaluation of qualitative overall acne severity. To accomplish this, the global assessment scale should be an ordinal scale with approximately five severity grades (reported only in integers, e.g., 0 to 4). Each grade should be defined by a distinct and clinically relevant morphologic description that minimizes interobserver variability. The grades on the scale should be sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. Photographic examples of each grade that have been agreed upon with the Agency before their use may be provided to investigators. It is recommended that measures to ensure blinding of investigators as to any previous or baseline scores with each evaluation be submitted for review by the Agency. For consistency, it is important that the same IGA scale be used throughout the study, including study enrollment, evaluation at endpoint, and for assessment of relapse. The Agency recommends that each subject’s improvement be verifiable (e.g., via photographic records of baseline and assessment time point) by Agency staff for auditing purposes. Table 1 is an example of an IGA scale that may be useful.

**Table 1. Sample IGA Scale for Acne Vulgaris**

<b>Grade</b>	<b>Description</b>
<b>0</b>	Clear skin with no inflammatory or noninflammatory lesions
<b>1</b>	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
<b>2</b>	Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
<b>3</b>	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
<b>4*</b>	Severe; greater than Grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

\* The Case Report Forms for acne studies can allow for reporting by investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris patients not include patients with nodulocystic acne. Patients who worsen beyond Grade 4 are to be described in the safety evaluation.

For assessment of efficacy, the Agency recommends that the IGA scale be dichotomized to *success* or *failure* using one of the following two criteria to be selected *a priori*.

- 1) **Clear or almost clear (Grades 0 or 1) as success:** Success is defined as “Clear” (Grade 0) or “Almost clear” (Grade 1) at the prespecified primary time point. For patients whose baseline score is Grade 2, the clinically meaningful criterion for IGA success is achieving a score of Grade 0 at the prespecified primary time point because of limitations inherent to an ordinal scale.
- 2) **Two grade improvement as success:** Success is defined as improvement of two grades from the baseline score at a prespecified primary time point. Since under

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377 this alternative definition of success not all subjects with “Severe” (Grade 4) acne  
378 will achieve the “Clear” or “Almost clear” state, if the product under study is  
379 approved, these outcomes would provide useful information in product labeling.  
380

381 We recommend that the IGA success criterion not selected *a priori* for primary  
382 evaluation be evaluated as a secondary endpoint. A study that fails on the primary IGA  
383 success criterion selected would not be rescued with the other success criterion, as this  
384 would not control for Type I error.  
385

386 For targeted acne therapy (i.e., treatment of inflammatory or noninflammatory lesions of  
387 acne alone), the IGA selected for use may modify emphasis for the lesion type not being  
388 evaluated.  
389

390 Applicants are encouraged to discuss other alternative IGA grading scales and study  
391 designs with the Agency before implementation.  
392

### 393 2. *Lesion Counts*

394

395 For the acne vulgaris indication, noninflammatory and inflammatory acne lesion counts  
396 are co-primary endpoints along with the IGA. When counting facial acne lesions, it is  
397 important that all lesions be counted, including those present on the nose.  
398

399 Even if the indication is limited to only one type of lesion (i.e., either noninflammatory or  
400 inflammatory lesions of acne), as described in Section III.A., Clinical Considerations, we  
401 recommend obtaining lesion counts for both types, but only declaring one as primary in  
402 the prespecified analysis plan.  
403

### 404 **B. Patient-Reported Outcomes**

405

406 The Agency is interested in *patient-reported outcome* information; however, such  
407 information should not be used as a substitute for objective data or as a surrogate for  
408 efficacy. For patient-reported outcome assessments, objective measures could be helpful  
409 tools, which may inform both the patient and clinician.  
410  
411

## 412 **V. DATA ANALYSIS**

413

414 It is important that the tools for statistical evaluation be appropriate for analysis of the  
415 efficacy endpoints. We recommend that the statistical analysis plan prespecify the  
416 primary efficacy variables, the study population, the hypothesis to be tested, and the  
417 statistical methodology to be used. It is important to consider the following points in the  
418 statistical analysis plan:  
419

420 1) The primary efficacy analyses for an acne indication should be:

421 a) Change from baseline in the inflammatory lesion count;  
422

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- 423           b) Change from baseline in the noninflammatory lesion count; and  
424           c) The proportion of success according to the dichotomized IGA.

425

426           Secondary efficacy variables should be those clinically relevant outcomes that  
427           support the validity of the primary efficacy variables.

428

- 429           2) For a general acne indication, we recommend the test drug be superior to its  
430           vehicle with respect to change, both in inflammatory and noninflammatory  
431           lesions, in addition to success according to the IGA (see above). It is also  
432           important to provide secondary analysis for percent change of lesion counts.

433

434           On the other hand, for an acne indication specific to a certain lesion type (see  
435           Section III.A.3., Targeted Acne Therapy), we recommend the test drug be  
436           superior to its vehicle with respect to the specified lesion type, and be noninferior  
437           to its vehicle for the other lesion type. It is important that the noninferiority  
438           margin be discussed and agreed upon with the Agency before study initiation. In  
439           addition, it is important to demonstrate superiority for success according to the  
440           IGA.

441

- 442           3) Prespecification of the statistical analysis is a key factor for obtaining consistent  
443           and convincing evidence of product efficacy, as data-driven analyses should not  
444           be used to support efficacy claims. We recommend the protocol have sufficient  
445           description of the statistical analyses of the primary efficacy endpoints so that an  
446           independent statistician could perform the analyses in the protocol. The  
447           description should include: specifying the hypotheses to be tested, indicating the  
448           level of significance to be used, and whether it is 1- or 2-sided, denoting the  
449           mathematical expression of the statistical models, and identifying methods for  
450           controlling Type I error rates for multiplicity or interim analyses if needed.

451

- 452           4) It is important that the protocol prospectively identify the covariates to be used in  
453           the analysis. We recommend using all prespecified covariates that are selected. It  
454           is also important that the number of covariates be kept to a minimum and limited  
455           to those whose influence on the outcome is suspected to be strong, such as  
456           stratification factors like study center.

457

- 458           5) We recommend addressing in the protocol possible center-by-treatment  
459           interaction along with planned sensitivity analyses to ensure robustness of the  
460           efficacy results.

461

- 462           6) If multiple assessments are taken (e.g., over time) it is important that the protocol  
463           prespecify how they will be evaluated for efficacy. If the claim is that a win  
464           occurs if any assessment wins, an adjustment needs to be made for multiplicity,  
465           but, if a win occurs only if all assessments win, no adjustment in significance  
466           level is warranted. We recommend that the method for multiplicity adjustment be  
467           planned and specified in the protocol. This would also include assessments for  
468           any validated patient-reported outcome endpoints.

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- 7) If interim analyses are planned, it is important that the protocol prespecify early stopping rules and penalties for such interim analyses.
- 8) We recommend provisions be made for analysis of clinically relevant secondary endpoints and subgroup efficacy analysis, along with safety evaluations. A multiplicity adjustment could be appropriate if the efficacy results from multiple secondary endpoints are intended to appear in the label.
- 9) It is important that the study protocol clearly define the study population to be analyzed, and provisions be made to handle dropouts (see Section V.A., Handling Dropouts). We recommend efficacy evaluation be carried out for the intent-to-treat (ITT) population, defined as all subjects randomized and dispensed study medication. We also recommend that a supportive analysis be carried out for the per-protocol (or completers) population and criteria for defining the per-protocol population be specified in the protocol.

**A. Handling Dropouts**

We recommend that efficacy and safety evaluation be carried out on all patients randomized and dispensed study medication. Every effort should be made to follow all enrolled subjects until the end of the study and until the resolution of any adverse event. However, in clinical trials, it is anticipated that a certain percentage of enrolled subjects will drop out.

Dropouts are common in acne trials and lead to information loss. It is unlikely that dropouts occur randomly, and they rarely occur completely independent of the treatment being tested, so there is always the possibility that dropouts introduce bias. The extent of this bias is expected to be related not only to the magnitude of the information loss due to dropout but also to the distribution of the dropouts among the various treatment arms. Several methods for handling dropouts have been proposed, but none is fully adequate.

- 1) The Agency’s current approach for acne vulgaris trials is based on using the intent-to-treat analysis with imputation of the last observation carried forward (ITT/LOCF), along with the per-protocol (completers) analysis. Although consistency in efficacy findings from the two analyses can increase confidence in the efficacy results, this does not resolve the problem of handling dropouts. The LOCF might not be the optimal approach for handling dropouts; however, it is frequently applied because of simplicity. If other or additional approaches for handling dropouts are proposed, we recommend they be prespecified in the protocol.
- 2) It is important that the effect of dropouts be addressed in all clinical trials and analyses, and analyses be carried out to demonstrate that the study conclusions are robust with regard to handling dropouts. An approach that can be used to check robustness of study findings is the worst-case rule (assigning the best possible

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515 score to all dropouts on placebo arm and the worst score to all dropouts on the  
516 active arm and then performing an analysis including these scores).

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### **B. Data Quality and Format**

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520 We recommend that all data from clinical trials be validated and their quality assured.

521 We also recommend that all data be submitted in electronic format per Agency guidance.<sup>5</sup>

522 It is important to consider the following points during database formulation:

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- 524 1) In addition to efficacy and safety data, it is important that demographic and  
525 baseline data be submitted to the Agency. It is also important that data for  
526 derived variables be provided along with the algorithm to generate these  
527 variables.
- 528
- 529 2) Efficacy and safety summaries can be consolidated. We recommend data from  
530 multiple studies use the same format, so that data from one trial can be easily  
531 merged with data from another to allow subset analyses based on gender, age,  
532 race, and, when appropriate, other subgroups.
- 533
- 534 3) Electronic photographic records should be submitted to the Agency such that they  
535 can be readily evaluated (e.g., sufficient resolution to allow for clinical re-  
536 evaluation), clearly labeled (e.g., with regard to subject, study number, center, and  
537 time taken), and organized in a retrievable fashion for storage and archiving  
538 purposes.
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<sup>5</sup> See guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations* and guidance for industry *Providing Regulatory Submissions in Electronic Format — NDAs* (<http://www.fda.gov/cder/guidance/index.htm>)



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