An Investigator’s Perspective on Practical Issues and Challenges in Conducting Clinical End Point Studies

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Endpoints in Clinical Trials

- Most trials will measure many endpoints

- **Endpoints used in clinical trials:**
  - Objective vs. subjective
  - Landmark vs. time-to-event
  - Binary (cure vs. failure) vs. continuous (mean % change from baseline)
  - Single event vs. composite
  - Cause-specific vs. all-cause
  - Combined endpoint
  - Clinical vs. surrogate

- **Surrogate Endpoints:**
  - Clinically important endpoint may be difficult to measure
  - Surrogate endpoint, or marker, may be more objective than clinical endpoints
  - Measured reliably, simply, and without invasive procedures
  - Surrogates are difficult to validate (correlate with clinical endpoint or change in clinical endpoint)
Endpoints Selection

- **Appropriate Endpoints depend on:**
  - Phase of the trial/development
  - Disease
  - Characteristics of measure
  - Therapy, dosage and dose regimen
  - Feasibility
  - Questions to be answered by trial
  - Measures taken to minimizing bias
  - Treatment groups (drug & control)

- **Choice of Endpoints has an effect on:**
  - Design
  - Conduct
  - Analysis
  - Interpretation
Characteristics of a Good Endpoint

- Objective
- Reproducible
- Sensitive/specific
- Unbiased
- Clinically relevant
- Chosen a priori
- Easy to identify, no evaluator judgment needed
- Easy to interpret
- Free of errors of measurement
- Stable
- Observable independent of Rx assignment
Clinical Endpoint Studies

- Clinical endpoint studies are list accurate, sensitive and reproducible. They are expensive and time consuming.

- Well-controlled clinical endpoint studies are acceptable for the demonstration of bioequivalence if:
  - Measurement of the drug or its metabolites in blood, biological fluids or tissues is inappropriate or impractical
  - There are no appropriate pharmacologic end-points to monitor

- A parallel group design with three treatment groups is usually used:
  - Test (generic) product
  - Positive control (reference listed drug (RLD)/pioneer product)
  - Placebo (or negative) control (to confirm the sensitivity or validity of the study)
Atopic dermatitis (AD) has a wide spectrum of dermatological manifestations and there is disagreement about its definition
  – Uniformity in the use of diagnostic criteria for AD is lacking
  – Clinical studies require valid diagnostic criteria for reliable and reproducible results.

The U.K. diagnostic criteria are the most extensively validated
  – Pruritus + 3 minor criteria

The Hanifin and Rajka diagnostic criteria widely used
  – Patients Must have three or more Major criteria and three or more Minor criteria

Suggested Universal Criteria for AD by American Academy of Dermatology
  – Essential features - must be present, associated features, exclusions

The reference standard likely to classify AD correctly is the clinical diagnosis by an experienced dermatologist
Study Design

■ Primary objective of the study:
  – To establish the therapeutic bioequivalence of test product to reference product and to show superiority to vehicle in the treatment of moderate to severe AD
  – Success defined as a grade 0 or 1 on ISGA after 14 days of treatment

■ Secondary objective of the study:
  – To compare the AE profiles
  – % change in BSA, EASI and ISGA after 14 days of treatment

■ Regimen:
  – BID (two times a day)

■ Randomization:
  – Patients are randomly assigned to test, reference and test vehicle (placebo)
  – 2:2:1 ratio

■ Visit schedule:
  – Visit 1 (day 1), Visit 2 (day 5), Visit 3 (day 15)
Instrument Selection

- Clinical scores used to assess the severity of AD rely entirely on subjective criteria to evaluate the severity of lesions and the extent of involvement.

- EASI (The Eczema Area and Severity Index – evaluates disease extent and clinical signs)

- BSA (rule of nines, computer-assisted estimates)

- ISGA (Investigator's Static Global Assessment) is a static assessment of disease status at the time of evaluation and it does not incorporate the sum of individual signs and symptoms:
  - It does not have clear distinction between the score 1 that is “almost clear” and represents the cure and score 2 that is “mild” and represents no cure.

  **VS.**

- **Improvement rate:**
  - Rate of patients with at least 50% (i.e. at least moderate) improvement according to the Physician's global evaluation of clinical response between Baseline and the Day 14.
### ISGA

#### Score for AD
<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong> Clear</td>
<td>Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting</td>
</tr>
<tr>
<td><strong>1</strong> Almost Clear</td>
<td>Trace, faint pink erythema with almost no induration/papulation, no oozing/crusting</td>
</tr>
<tr>
<td><strong>2</strong> Mild Disease</td>
<td>Faint pink erythema with mild induration/papulation, no oozing/crusting</td>
</tr>
<tr>
<td><strong>3</strong> Moderate Disease</td>
<td>Pink-red erythema with moderate induration/papulation, and there may be some oozing/crusting</td>
</tr>
<tr>
<td><strong>4</strong> Severe Disease</td>
<td>Deep/bright red erythema with severe induration/papulation, with oozing/crusting</td>
</tr>
</tbody>
</table>

#### Score for Acne
<table>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong> Clear</td>
<td>clear skin with no lesions</td>
</tr>
<tr>
<td><strong>1</strong> Almost Clear</td>
<td>rare non-inflammatory lesions</td>
</tr>
<tr>
<td><strong>2</strong> Mild</td>
<td>some non-inflammatory lesions with no more than a few inflammatory lesions but no nodular lesions</td>
</tr>
<tr>
<td><strong>3</strong> Moderate</td>
<td>up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than 1 small nodular lesion</td>
</tr>
<tr>
<td><strong>4</strong> Severe</td>
<td>up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions</td>
</tr>
<tr>
<td><strong>5</strong> Very Severe</td>
<td>many non-inflammatory and inflammatory lesions and more than a few nodular lesions. May have cystic lesions</td>
</tr>
</tbody>
</table>

#### Score for Psoriasis
<table>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong> Clear</td>
<td>minor residual discoloration; no erythema/scaling/plaque thickness</td>
</tr>
<tr>
<td><strong>1</strong> Almost Clear</td>
<td>occasional fine scale/faint erythema/barely perceptible</td>
</tr>
<tr>
<td><strong>2</strong> Mild Disease</td>
<td>fine scales predominate; light red coloration/mild</td>
</tr>
<tr>
<td><strong>3</strong> Moderate Disease</td>
<td>coarse scales predominate; moderate red coloration/moderate</td>
</tr>
<tr>
<td><strong>4</strong> Severe Disease</td>
<td>thick tenacious scale predominates; deep red coloration/severe</td>
</tr>
</tbody>
</table>
Atopic Dermatitis

Source: hardinmd.lib.uiowa.edu
Patient Selection

- **Inclusion Criteria:**
  - Confirmed diagnosis of atopic dermatitis using the diagnostic criteria
  - IGSA score of 3 (moderate) or 4 (severe)
  - Affected Body Surface Area (BSA) of at least 20%
  - Eczema Area and Severity Index (EASI) score of at least 15

- **Exclusion Criteria:**
  - Clinically infected atopic dermatitis
  - Any dermatological condition other than atopic dermatitis
  - History of allergy or sensitivity to investigational product
  - Current diagnosis or history or any disease, which in the Investigators opinion would contraindicate the use of IP

- Patients from the Investigator’s database
- **Less severe population**
- **Smaller BSA**
  - Division of Dermatologic and Dental Products (DDDP) has generally recommended a BSA of at least 20% for moderate to severe AD and a grade of 3 to 4 on a five grade Investigator’s Static Global Assessment Scale (ISGA)
- **Smaller % head and neck involvement at the baseline**
Challenges at the Site Level

- Site selection
  - Location of sites (seasonal effect, affiliations)

- Number of sites

- Number of patients per site:
  - No single site should provide large fraction of participants
  - Outliers in the number of patients can greatly jeopardize the data

- Site training:
  - No single investigator or site should provide a disproportionate favorable effect

- Intra and inter-rater reliability
  - Variability between investigators in a multicenter study

- Competing studies at site:
  - Different diagnostic criteria same indication
  - Different severity same indication
  - Different indication
Challenges in Assessing Treatment Effects

- The choice of a treatment should be tailored to each patient based on:
  - Potency
  - Vehicle
  - Lesion location
  - Patient age
  - Season
  - Environment
  - Socioeconomic class
  - Prior medication(s)
  - Presence or absence of infection
  - Patient preferences

- Therapy not suitable
- Duration of treatment
- Dose:
  - Different spreading on the skin (a thin layer to target area)
  - Dosing diary (dates and times)

- Drug used should be weighed and documented:
  - The study tube should be weighed before and after the dose application
  - The study tube should be weighed at each visit

- Different shape or packaging might unblind the product
Compliance of Patients

- Concomitant Medications
- Concomitant use of moisturizers or sunscreens
- Overall compliance of patients
- Oral versus topical medications
- Regimen
- Wash out of topical medications
  - Antifungal products require wearing protective socks and shoes
- Medical History
- Adverse Events
- Topical steroid phobia is common among patients with AD and has an impact on adherence with topical steroids
- Temperature excursions while medication with patients
Trial Duration

- **Shorter duration of the study:**
  - Much lower drop out rate in the vehicle group
  - Shorter investigational product exposure, before any significant success proportion is expected.
  - Most likely to detect differences between test and reference products.

- **OOW assessments and visits**

- **Systemic exposure decreases as the lesion heals**