Safety and Efficacy Comparison Trial

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Clinical Trial: Objective

- Compare the efficacy and safety of the new formulation of isotretinoin administered once daily without food to currently marketed Accutane administered twice daily with food

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Clinical Trial

- Focus on design features and study results that inform 3 issues:
  - Dose Ranging
  - Adverse Events
  - Management of "Switch-Over" Risks

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Dose-Ranging

- Isotretinoin exposure in the Accutane arm was significantly higher than in the new formulation arm
- If the trial showed equivalent efficacy, it would suggest that 1 mg/kg/day Accutane with food is not the minimum effective dose

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Dose-Ranging: Efficacy Results

- Comparison between the new formulation at 0.4 mg/kg/day without food to Accutane® at 1 mg/kg/day with food

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Efficacy Results

- The new formulation was *marginally* less effective as measured by proportion of patients with at least 90% reduction in nodules

- Therapeutic equivalence, however, is supported by
  - percent reduction in nodules
  - equivalent global assessments
  - equivalent short-term need for retreatment *in the overall population*

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Need for Retreatment

- Assessed at week 36
- Need for retreatment is of particular concern for pediatric patients and women
- Pediatric-aged patients may have higher acne relapse rates

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Results

	Accutane	New Formulation
at least 90% reduction in nodules	77 %	64%
required retreatment	14%	26%

Note: there were 92 patients per arm ages 12-17

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Results:
Women Using Ortho Tri-Cyclen®

	Accutane	New Formulation
at least 90% reduction in nodules	84 %	57 %

Note: This sample size is too small for analysis (19 and 21 patients respectively)

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Equivalent Efficacy

Although subset results suggest that Accutane® *may* have been slightly more efficacious than the new formulation *at the dosage tested*, overall trial results support therapeutic equivalence

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Efficacy Conclusions

- Isotretinoin exposure in the Accutane® arm was higher than in the new formulation arm
- Therefore, efficacy equivalence suggests that 1 mg/kg/day Accutane may be unnecessarily high for many patients

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Efficacy Conclusions

- The minimum effective dose is of clinical importance because isotretinoin use is associated with serious adverse events
- Even "non-serious" side effects can lead to discontinuation of effective treatment for severe scarring acne

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Efficacy Conclusions

- Even if the tested dose of the new formulation (0.4 mg/kg/day) is close to the minimum effective dose, we do not know:
  - the range of dosing to recommend for patients who require dose escalation; or
  - the safety profile for higher doses

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Issue 2: Adverse Events

- The total safety population for the new formulation is 583 subjects:
  - 300 in the clinical equivalence study
  - 283 in the short-term pharmacokinetic studies
- The submitted adverse event profile did not reveal events not previously observed in the safety database for marketed Accutane

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Early Terminations

- 16 from each treatment group withdrawn for adverse events
- 8 patients in each group "refused treatment"
- Lost to follow-up during the 20 week treatment phase:
  - 3.7% for the new formulation
  - 6.7% for Accutane

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Reasons for Withdrawal from Study

- While the proportion of patients withdrawn for adverse events was equivalent between arms, the reasons were not:

– NEW FORMULATION:	4 - psychiatric symptoms
– ACCUTANE:	0 - psychiatric symptoms

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Discontinuations for Psychiatric Adverse Events

- The number of discontinuations for psychiatric symptoms is probably a poor comparative measure of safety due to problems with protocol criteria for discontinuation
- There is no readily apparent reason for unbalance between arms

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Reported Psychiatric Adverse Events

- 11 psychiatric adverse events reported in the new formulation arm
- 1 in the Accutane® arm
- This disproportion is statistically significant and would be cause for concern

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Reported Psychiatric Adverse Events

- The reported numbers refer only to subjects who verbally complained of symptoms
- Patients answered four specific questions to determine if they had experienced any significant depression or insomnia since the last visit that "affected their work or ability to perform normal daily activities"
- Patients with 2 or more positive responses then filled out the depression inventory

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Reported Psychiatric Adverse Events

- If the following patients are included, the number with psychiatric "events" is equivalent:
  - Patients with verbal report of symptoms
  - Patients included in analysis by sponsor's consultants
  - Patients with no psychiatric adverse event recorded but:
    - answered "yes" to the BDI self-injurious behavior question
    - answered "yes" to at least 2/4 screening questions
    - and/or had BDI-II scores within a few points indicative of "severe" depression

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Assessment of Results: Psychiatric Adverse Events

- As with discontinuations, there is no readily apparent reason for the disproportion in *reporting* of psychiatric events
- Retrospective post-hoc analysis cannot eliminate the fact that the clinical judgment of doctors caring for patients in a trial underlies event reporting and discontinuation

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Assessment . . .

- The trial was neither intended nor designed to evaluate psychiatric effects
- The design and conduct of the trial preclude reliable case ascertainment or estimates of incidence
  - Bias against reporting AE due to efficacy of the drug
  - Recording of events and follow-up was variable

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Assessment . . .

- A chance finding for disproportion is consistent with:
  - Reported psychiatric events in the new formulation arm were not > the range in published literature for currently marketed Accutane (1-10%)
  - Lower serum levels of isotretinoin in the new formulation arm
  - Hypertriglyceridemia and mucocutaneous events were not more common in the new formulation arm

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Assessment . . .

- Requires assumptions:
  - Even if association with psychiatric events is causal, they may not track with non-psychiatric dose-related effects (dose threshold may be lower)
  - We are aware of no pharmacokinetic basis for greater CNS accumulation of the new formulation relative to currently marketed Accutane

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Assessment . . .

- Causality between psychiatric disease and isotretinoin use has *not* been established
- If there is no causal relationship, then the new formulation cannot be less safe than Accutane in this regard
- If studies *did* support a causal relationship, uncertainty would persist about the relative safety of the new formulation

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How Do the Two Formulations Compare for Other Important Adverse Events?

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Mucocutaneous Adverse Events (MAE)

- Profile is important because MAE are frequent cause of treatment discontinuation
- The mucocutaneous safety profile for the new formulation is comparable to Accutane® at the dosage tested

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Headache

- New Formulation:
  - Approximately equal frequency, but duration 2-5 days longer
  - Two cases characterized as "migraine"
  - One possible case of pseudotumor cerebri
- Accutane®
  - Three discontinuations

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Pregnancy

- One patient became pregnant while taking the new formulation
- The stated facts of the case do not suggest patient non-compliance with contraceptive measures
- One pregnancy among 244 female patients in the controlled setting of a trial for a known teratogen is of great concern

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Laboratory Abnormalities

- Hypertriglyceridemia Withdrawals
  - new formulation: 3
  - Accutane®: 6
- Relative increase in triglycerides
  - new formulation: 49%
  - Accutane®: 88%
- Findings are consistent with lower serum levels of isotretinoin in the new formulation arm

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Issue 3: Risks Associated with "Switch-Over"

- Inappropriate dosing
- Concurrent administration
- Confusion about capsule strengths on the prescription
- Uncertainty about bioavailability and actual drug exposure
- Misunderstanding about once daily administration and food instructions
- Potential for inappropriate substitution at the pharmacy

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Issue 3: "Switch-Over"

- A new TRADENAME *should*:
  - retain 18 years of recognition for this potent teratogen
  - clearly distinguish the two products if both are to be marketed

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Risk-Benefit Analysis

- There is no apparent pharmacokinetic basis to suspect that the new formulation would be less safe than current Accutane®
  - Drug Interaction
  - Psychiatric Adverse Events

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Risk-Benefit Analysis

- Given the unknowns and the switch-over risks, what does the new formulation offer patients?

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Risk-Benefit Analysis

- Sponsor's stated goal:
  - enhanced convenience/patient compliance
  - reduced intra-and inter-patient variability while retaining the efficacy and safety profiles of currently marketed Accutane®

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Risk-Benefit Analysis

- Because the food effect with Accutane® is so large, the new formulation reduces variability in serum levels of isotretinoin

- Benefit for patients would be dependent on equivalent (or better) safety and efficacy, since the impact of the convenience factor is likely to be small

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