

# Sample Size Determination in the Safety Evaluation of FVIII Products

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# Factor VIII

- Major safety concern
  - Inhibitor formation
- Sample size determination
  - Safety evaluation: Inhibitor formation

# Read My Lips

$$\begin{aligned}
 P[T_2 \leq t_2] &= P[T_1 - c_1(S) \leq t_2] \\
 &= P[T_1 - (S^2/n) \chi^{-1}(\alpha; k-1, \lambda_0(S, \delta)) \leq t_2] \\
 &= P[(1/\sigma^2)T_1 - (S^2/\sigma^2) \chi^{-1}(\alpha; k-1, \lambda_0(S, \delta)) \\
 &\quad \leq (n/\sigma^2)t_2] \\
 &= P[\chi^{-1}(\alpha; k-1, \lambda_0(S, \delta)) \leq \\
 &\quad (n/\sigma^2)t_2 + (S^2/\sigma^2) \chi^{-1}(\alpha; k-1, \lambda_0(S, \delta))]
 \end{aligned}$$

# A Big Question

How do we determine the sample size?

How do we  
determine the  
sample size?

# Question for a Statistician

What sample size do I need?

# n

- Study design?
- Study objective?

# Study Design

- Studies to date have lacked concurrent controls
- Relied on the “historical data”
- Compare the inhibitor formation rate (proportions) of the test product with an upper acceptable limit

# Study Objective

- Want to show that the inhibitor formation rate is low.
  - The true inhibitor formation rate of the test product  $<$  an upper acceptable limit
    - Not the observed inhibitor formation rate
    - Upper confidence limit  $<$  upper acceptable limit
- How low is low?
  - Upper acceptable limit = ???

# Upper Acceptable Limit

- 1%? Too low - Impossible to show
- 30%? Too high - Clinically unacceptable
- Need to make a cut somewhere in between
- Where?
- If the study succeeds (i.e., upper confidence limit  $<$  upper acceptable limit), then the true inhibitor formation rate of the test product is most likely to be much lower than the upper acceptable limit.

# Sample Size

- Sample size depends on
  - Upper acceptable limit: Smaller  $\Rightarrow$  Larger n
  - Confidence level: Higher  $\Rightarrow$  Larger n
  - Number of inhibitors that are allowed to be considered a success for the study: More  $\Rightarrow$  Larger n
- Rule of three
  - Simple and useful tool

# Rule of Three

- For a large  $n$  (e.g.,  $n \geq 20$ ), if no inhibitors are observed, then the one-sided 95% upper confidence limit  $\cong 3/n$ 
  - Does not apply if one or more inhibitors are observed
  - Works for 95% confidence level only
  - Works for large  $n$ , e.g.,  $n \geq 20$

# Example

- Upper acceptable limit: 10%
- Confidence level: 95%
- Rule of three: One-sided 95% upper confidence limit  $\cong 3/n$  (no inhibitors are observed)
- Set  $3/n = 10\%$ , then  $n = 30$
- More accurate:  $n = 29$
- If one inhibitor is observed out of 29 subjects, then the study fails.

# Sample Size (2)

Allowing no inhibitor			Allowing one inhibitor		
Confidence level	Upper acceptable limit		Confidence level	Upper acceptable limit	
	5%	10%		5%	10%
95%	59	29	95%	93	46
97.5%	72	36	97.5%	109	54

1/29; One-sided 95% upper confidence limit = 15%

1/46; One-sided 95% upper confidence limit = 9.90%

1/45; One-sided 95% upper confidence limit = 10.10%

# FDA's Current Thinking

- Analyses will be Intent-to-Treat
- The upper limit of the two-sided 95% confidence interval for the inhibitor formation rate  $< 6.8\%$ 
  - Same as one-sided 97.5% confidence level
  - Upper acceptable limit = 6.8%
- Why 6.8%?
  - Allow one inhibitor out of 80 subjects

# Inhibitor Formation Rate: Considerations

- Inhibitor formation rate depends on
  - Population: PTP or PUP
  - Definition of inhibitor formation
    - Lowest unacceptable inhibitor level
  - Duration of exposure: Number of exposure days (at least 50 in clinical trial)
  - Assays for detecting inhibitor formation
  - Others?
    - Subjects for discussions

# Upper Acceptable Limit: Considerations

- Depends on the inhibitor formation rate for the “historical data”
  - If the “Historical data” is 1% to 2%, then 6.8% may be too high
  - If the “Historical data” is 3% to 4%, then 6.8% may be reasonable
- Need to estimate the inhibitor formation rate for the “historical data”

# Why 6.8%?

- Where does 6.8% come from?
- Data driven
  - The upper limit of the two-sided 95% confidence interval for the inhibitor formation rate for observing one inhibitor out of 80 subjects is 6.77%.
  - To “pass” the outcome of one inhibitor out of 80 subjects, upper acceptable limit = 6.8%.
- Back calculation

# Summary

- Sample size
  - Confidence level
  - Upper acceptable limit
  - Number of inhibitors that are allowed
- Need to estimate the inhibitor formation rate for the “historical data” so that the upper acceptable limit can be determined.

# Two Interesting Topics

- Statistical power depends on
  - Upper acceptable limit
  - Confidence level
  - Sample size
  - True inhibitor formation rate
- If the study fails (the upper confidence limit  $>$  the upper acceptable limit), can we enroll more subjects?

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