CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-484

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-484
Name of drug:	Bravelle (puified urofollitopin) 75 IU
Applicant:	Ferring Pharmaceuticals, Inc
Indication:	Induction of ovulation and pregnancy in anovulatory infertile women
Documents reviewed	Statistical Volume 1.10
Project manager:	Archna Reddy, HFD-580
Clinical reviewer:	Ridgely Bennett, M.D. (HFD-580)
Dates:	Stamp Date: 21 Feb 2002
Statistical reviewer:	David Hoberman, Ph.D. (HFD-715)
Statistics team leader:	Mike Welch, Ph.D. (HFD-715).
Biometrics division director:	S. Edward Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, non-inferiority, lognormal distribution, Hodges-Lehman estimates

Background

The sponsor has conducted trial FPI FSH 2001-01 as a response to the Division's conclusion that the previously reviewed trial, FPI FSH 99-04, did not provide enough evidence that Bravelle was non-inferior to Follistim with respect to the number of retrieved oocytes, the primary clinical endpoint. The required non-inferiority margin has been the subject of discussion but no agreement has yet been made with the company at the time of this review. However, the Division sent the sponsor a letter finalized on February 5, 2002 recommending that the non-inferiority margin be 2.2 oocytes. This margin reflects a decrease of 20% from the mean of 10.9 oocytes. This review does not discuss the issue of which non-inferiority margin will eventually be adopted for this trial.

Design of Study

The current trial was randomized, and assessor-blinded with 13 centers in the US. The two treatment groups were subcutaneous Bravelle and subcutaneous Follistim. According to Modification #2, dated October 22, 2001, the goal of the study was to "show that the number of oocytes retrieved for purified FSH SC is within 4.1 of Follistim." Then, "Power calculations were performed based on alpha=.025 (a conservative value for alpha assuming a one-tailed test) and the power=80%". Calculations then led to a sample size of 62 per treatment group. The protocol also states that a *one-sided 95% confidence interval* will be used to determine whether the lower bound for the mean difference between Bravelle and Follistim excludes the mean of 4.1 oocytes fewer than Follistim's mean.

The protocol specifies one-way ANOVA and a supplementary ANCOVA using age and BMI as covariates as methods of analysis. Thus, the sponsor's major analyses do no account for 'center' as a factor in the design. There is no explanation for this omission.

Results

The trial randomized 60 subjects to each group. However, only 57 subjects received hCG in the Bravelle group and 59 in the Follistim group. For purposes of the ITT analysis, the sponsor assigned zero's to these four subjects. The Primary Efficacy Responder group included only the latter 116 subjects who received hCG.

The table below displays the results for the number of retrieved oocytes. The figures in parentheses refer to the Primary Efficacy Responder group.

	Mean	Std
Bravelle	11.8 (12.4)	6.3 (5.9)
Follistim	11.9 (12.1)	6.9 (6.8)

Using ANOVA (in this case, a two-sample t-test), the sponsor reports the lower bound of a one-sided 95% confidence interval from the difference in mean oocytes to be –2.1 for the ITT analysis

and –1.6 for the Primary Responder analysis. This reviewer has calculated that the respective lower bounds for the *two*-sided 95% confidence intervals are -2.5 and -2.0.
The table below displays the mean number of oocytes for each treatment group by center:

Mean # of Oocytes by Center

Center	N	Bravelle	N	Follistim
1	4	12.2500	6	9.8333
2	11	9.3636	10	9.1000
3	1	11.0000	2	8.0000
4	3	13.0000	2	7.5000
5	4	12.2500	5	21.0000
6	2	15.5000	0	.
7	5	13.4000	6	11.8333
8	2	22.0000	4	15.2500
9	7	10.2857	6	15.0000
10	5	12.8000	4	8.0000
11	2	13.5000	3	16.3333
12	8	12.6250	7	12.7143
13	3	16.3333	4	8.5000

Reviewer's Comments

When center #6 is deleted (2 subjects) and the analysis repeated with center in the ANOVA, the lower bound using the Primary Responder subgroup is –2.1.

Examination of this count data reveals that it is not symmetrically distributed, let alone normally distributed. The table below displays the stem-and-leaf diagrams of the raw data.

Follistim

Stem Leaf	#	Stem-and-leaf diagram

Bravelle

```
Stem Leaf      #          Stem-and-leaf diagram
              32 0                1              0
              30
              28
              26
              24 0                1              |
              22 0                1              |
              20 00000            5              |
              18 0000             4              |
              16 0000             4              +------+
              14 000              3              |      |
              12 00000000         8              |  +   |
              10 00000000         8              *------*
               8 0000000000000   13              +------+
               6 000              3                 |
               4 00000            5                 |
               2 0                1                 |
                 ----+----+----+----+
```

The figures below display the stem-and-leaf diagrams of the log-transformed counts. Note that the data may be samples from lognormal distributions with large variance.

Follistim

```
              34 3                1                 |
              33 37               2                 |
              32                                    |
              31 48               2                 |
              30 099              3                 |
              29 4                1                 |
              28 333999           6              +------+
              27 1177             4              |      |
              26                                 |      |
              25 666              3              |      |
              24 008888888        9              *------*
              23 0000             4              |  +   |
              22 000              3              |      |
              21                                 |      |
              20 88               2              |      |
              19 555              3              |      |
              18                                 |      |
              17 99999            5              +------+
              16 111111           6                 |
              15                                    |
              14                                    |
              13 999              3                 |
              12                                    |
              11 00               2                 |
              10
                 ----+----+----+----+
             Multiply Stem.Leaf by 10**-1
```

APPEARS THIS WAY
ON ORIGINAL

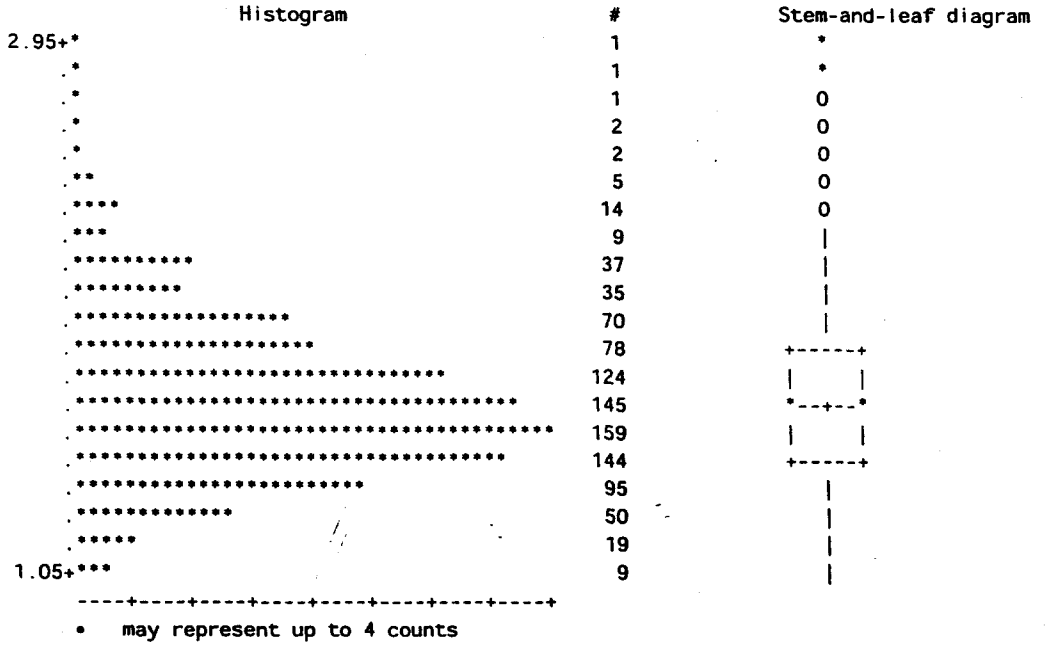
Bravelle

Stem Leaf

	Stem-and-leaf diagram	
34 7	1	
33		
32 2	1	
31		
30 000049	6	
29 44	2	
28 33399	5	+------+
27 117	3	| |
26 4	1	| |
25 666666	6	| |
24 0000088	7	*--+--*
23 000	3	| |
22 00000	5	| |
21		| |
20 88888888	8	+------+
19 55	2	|
18		|
17 9	1	|
16 11	2	|
15		|
14		|
13 999	3	|
12		|
11 0	1	|
10		
----+----+----+----+		

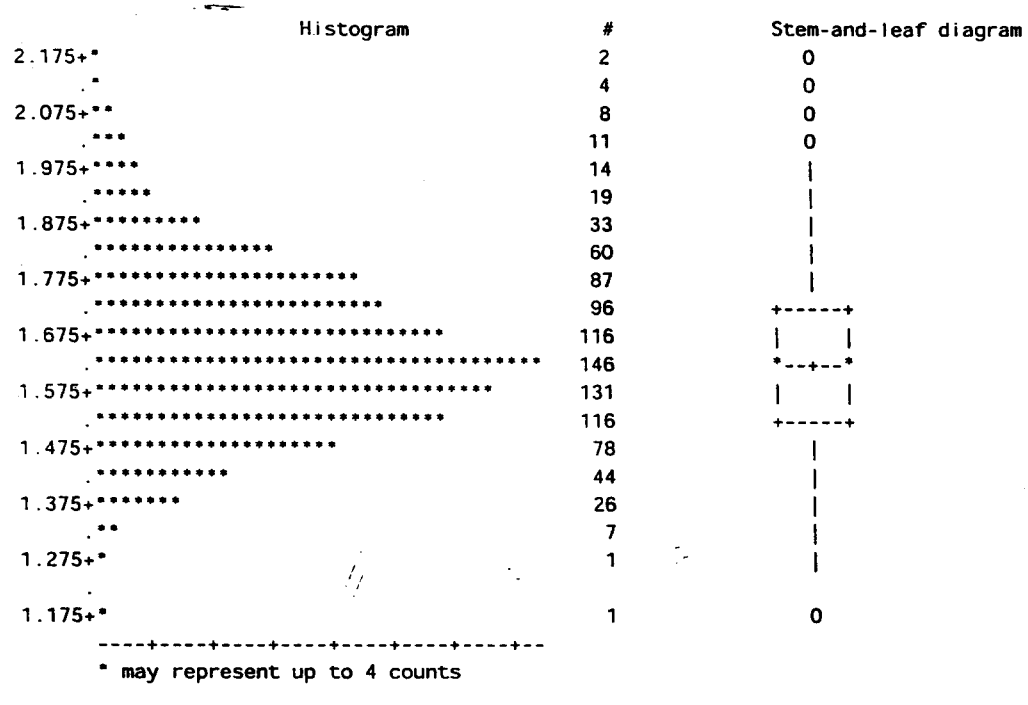
Multiply Stem.Leaf by 10**-1

To illustrate the problem with using the central limit theorem to calculate confidence intervals, this reviewer simulated 1000 samples of 60 observations each from the lognormal distribution generated by exponentiating standard normal deviates. The figure below displays the stem-and-leaf diagram of that simulation.



Note that there is still a marked skewness which calls into question the use of the normal distribution for the purpose of using its percentiles to construct confidence intervals. Further simulations of identical lognormal distributions resulted in only 82% coverage of zero when 95% confidence intervals were constructed for the true difference (viz, zero) between the means of the distributions.

Using simulations with 200 observations instead of only 60, the figure on the next page displays in a much more normally distributed stem-and-leaf diagram.



These results are in close agreement with the conclusions of Rand Wilcox in his book Fundamentals of Modern Statistical Methods, 2001.

In view of these observations, this reviewer carried out alternative analyses:

1. Compute the 95% confidence interval for the ratio of the geometric means: Bravelle/Follistim. Using the log transform of the counts, the lower bound for this ratio is .88, indicating a worst case of a 12% decrease in the geometric mean with Bravelle.

2. Using the Hodges-Lehman procedure, the exact Hodges-Lehman confidence interval for the difference between the medians of the raw distributions is (-2.0, 3.0) using both the ITT data set (assigning 4 zero's to non-hCG subjects) and the Primary Responder subgroup. This is an interesting result because this confidence interval has essentially 95% coverage of the true mean instead of 82%, but the lower bound is essentially the same as that using the raw distribution and then relying on the central limit theorem. This may have occurred as result of a substantial number of tied counts in the data set.

Conclusion

Despite potential problems with the sponsor's analysis in view of the distributions of the actual data, the data provide evidence that the mean number of oocyes retrieved with Bravelle is no more than 2 oocytes less than the mean when using Follistim.

/S/

David Hoberman, Ph.D.
Mathematical Statistician

cc:
Arch NDA# 21-484
HFD-580
HFD-580/RBennett, SSlaughter, DSpell-LeSane
HFD-715/DHoberman, MWelch, ENevius, CAnello

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mike Welch
11/7/02 11:58:32 AM
BIOMETRICS
Submitted by M.Welch for D.Hoberman. Concur with review.

S. Edward Nevius
11/7/02 02:54:36 PM
BIOMETRICS
Concur with review.

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Statistical Review (Dissolution/Stability)

This new drug application did not require a statistical review of dissolution/stability.

12/08/02

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Statistical Review (Carci Studies)

No statistical review of Carci studies required.

AR 12/08/02