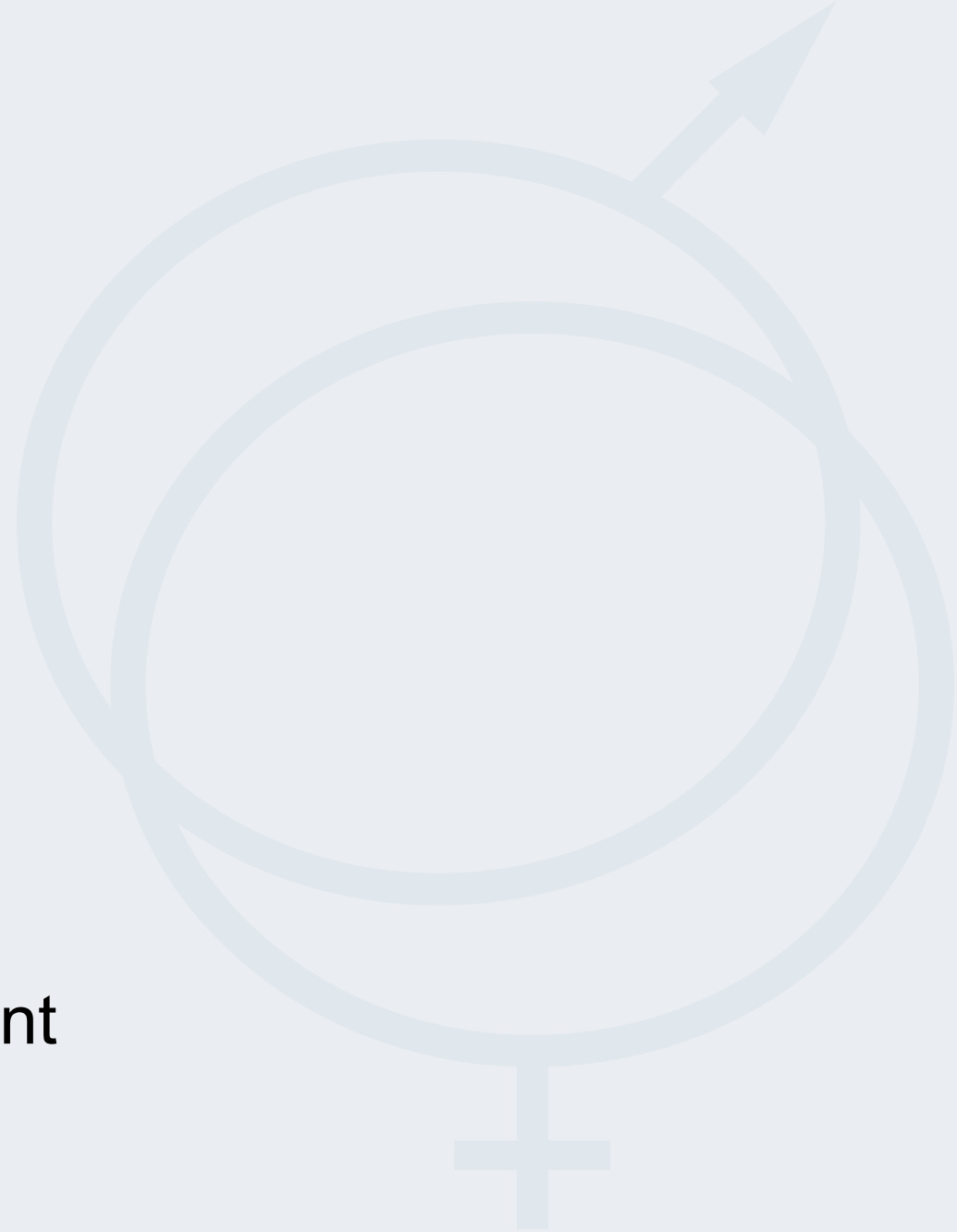
ZA-301

Site 9 Evaluation

Blinded Assessment



Repros Disclaimer

Any statements made by the Company that are not historical facts contained in this release are forward-looking statements that involve risks and uncertainties, including the ability to raise additional needed capital on a timely basis in order for it to continue to fund development of its Androxal® and Proellex® programs, have success in the clinical development of its technologies, the reliability of interim results to predict final study outcomes, and such other risks which are identified in the Company's most recent Annual Report on Form 10-K and in any subsequent quarterly reports on Form 10-Q. These documents are available on request from Repros Therapeutics or at www.sec.gov. Repros disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

ZA-301 Phase 3 Protocol Under an SPA

- **Phase 3 pivotal studies being conducted under SPA**
  - 2 identical trials (BMI > 25, Age ≤ 60)
    - 152 subjects in each trial (114 on Androxal, 38 on placebo)
      - Men with morning T<300 ng/dL assessed twice on two separate days
    - Up-titration from 12.5 to 25
    - 3 month duration
  - Co-Primary endpoints
    - 75% of men achieve T in normal range (300-1040 ng/dL)
    - Non inferior to placebo regarding change in sperm counts

Excerpt: FDA SPA Minutes

1) Proportion of subjects with average serum concentration (Cavg) for T in the normal range (i.e. serum T of 300 ng/dL – 1040 ng/dL).
2) Proportion of subjects with a 50% or greater decrease in sperm concentration from baseline to endpoint.
To demonstrate efficacy with regards to the first endpoint, at least 75% of subjects in the Androxal group should achieve a Cavg for T in the normal range with the lower bound of the 95% confidence interval not below 67%. At least 100 Androxal subjects would be required to demonstrate a point estimate of 75% or better.
For the second endpoint, Androxal should be non-inferior to placebo with respect to the difference in responder rates We have found a 20% non-inferiority margin to be acceptable in prior similar trials.
Values for serum T and sperm concentration at baseline and endpoint should be based on at least two assessments. Semen sampling at each time point (baseline and endpoint) should be separated by at least 48 hours.
Cmax is an important safety issue. The percentage of patients with Cmax above the following three pre-determined limits (listed below) should be a secondary endpoint:

- *Cmax>1500 ng/dL*
- *Cmax>1800 ng/dL and <2499 ng/dL*
- *Cmax>2500 ng/dL*

Outcome Sensitivity

If the response rate is greater than 75%, then the required sample size to have the lower limit exceed 67% decreases considerably. Here's a table with the minimum number of subjects that would be required to have the lower limit exceed 67% for each responder rate. The last column is what the lower limit of the 95% CI will be with N=113.

Responder Rate	N	Lower Limit of 95% CI	Lower Limit of 95% CI with N=113
75%	113	67.02%	67.02%
80%	37	67.11%	72.62%
85%	16	67.50%	78.42%
90%	7	67.78%	84.47%
95%	3	70.34%	90.98%

Consulting Statistician Comments

Assuming that 1% of the placebo group and 10% of the Androxal group experience a 50% or greater decrease in sperm concentration, and a 1:1 randomization ratio, 53 subjects per group (106 subjects total) would be required to show that Androxal is non-inferior to placebo in causing an abnormal sperm count at the 0.05 significance level and assuming a non-inferiority limit of 20%. If you use a 2:1 randomization ratio, 84 subjects in the Androxal group and 42 subjects in the placebo group (126 subjects total) would be required. If you went with 150 subjects total and a 1:2 randomization ratio (100 Androxal + 50 placebo), that would give you 87% power.

- Proportion of subjects with a 50% or greater decrease in sperm concentration from baseline to endpoint.

Using a 3:1 or 4:1 randomization ratio doesn't reduce the required placebo group sample size significantly but it does inflate how many subjects in the Androxal arm would be required (3:1 requires 114 Andoxal/38 placebo/152 total and 4:1 requires 144 Androxal/36 placebo/180 total).

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- Mean Age
  - Site 9 (n=40): 45.9
  - Other 16 sites: 46.6
- Mean BMI
  - Site 9: 29.6
  - Other 16 Sites: 31.9

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- Baseline Sperm Concentration
  - Site 9: 17.6×10^6 sperm/mL
  - Other 16 Sites: 80.7×10^6 sperm/ml
- Baseline T
  - Site 9: 167 ng/dL
  - Other 16 Sites: 202 ng/dL

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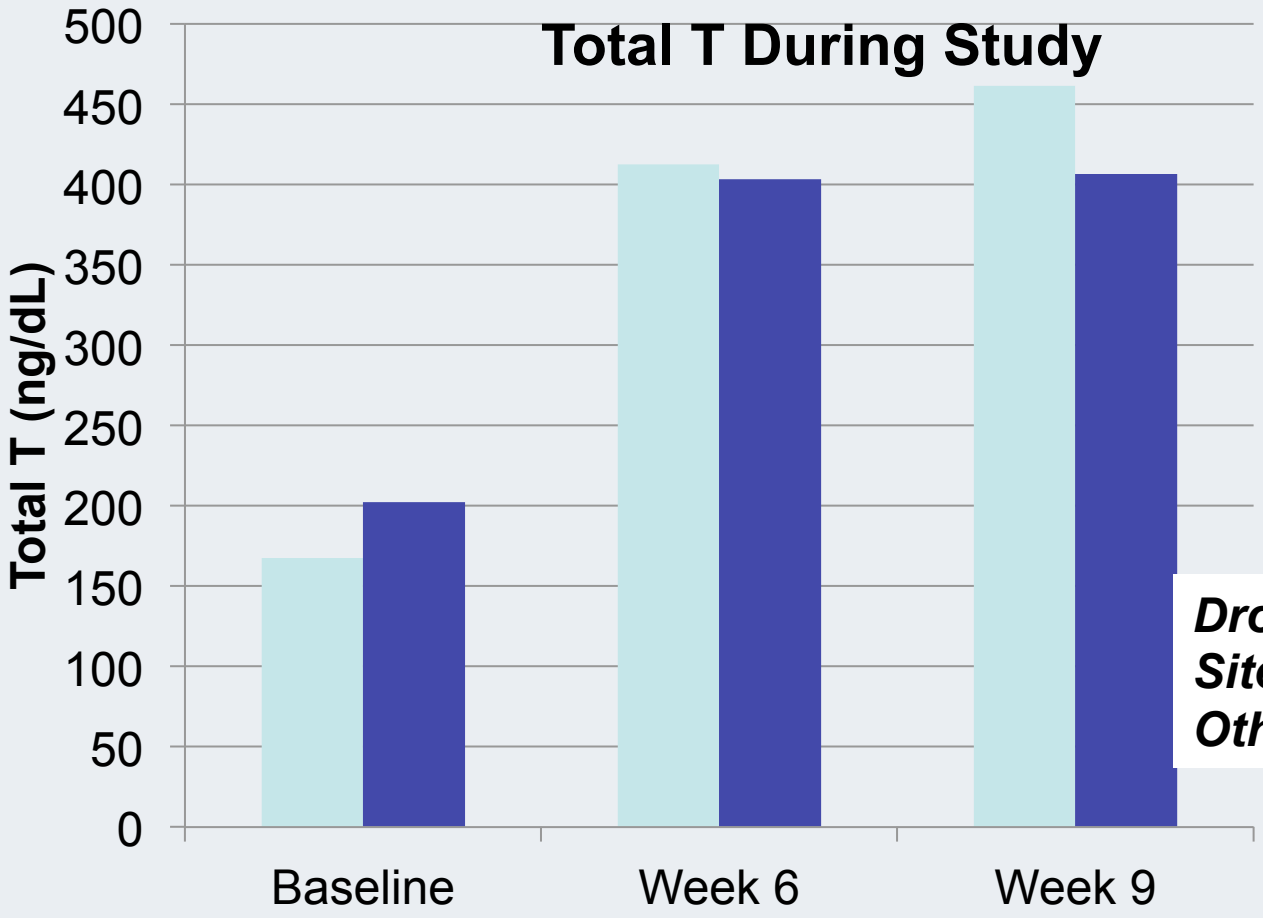
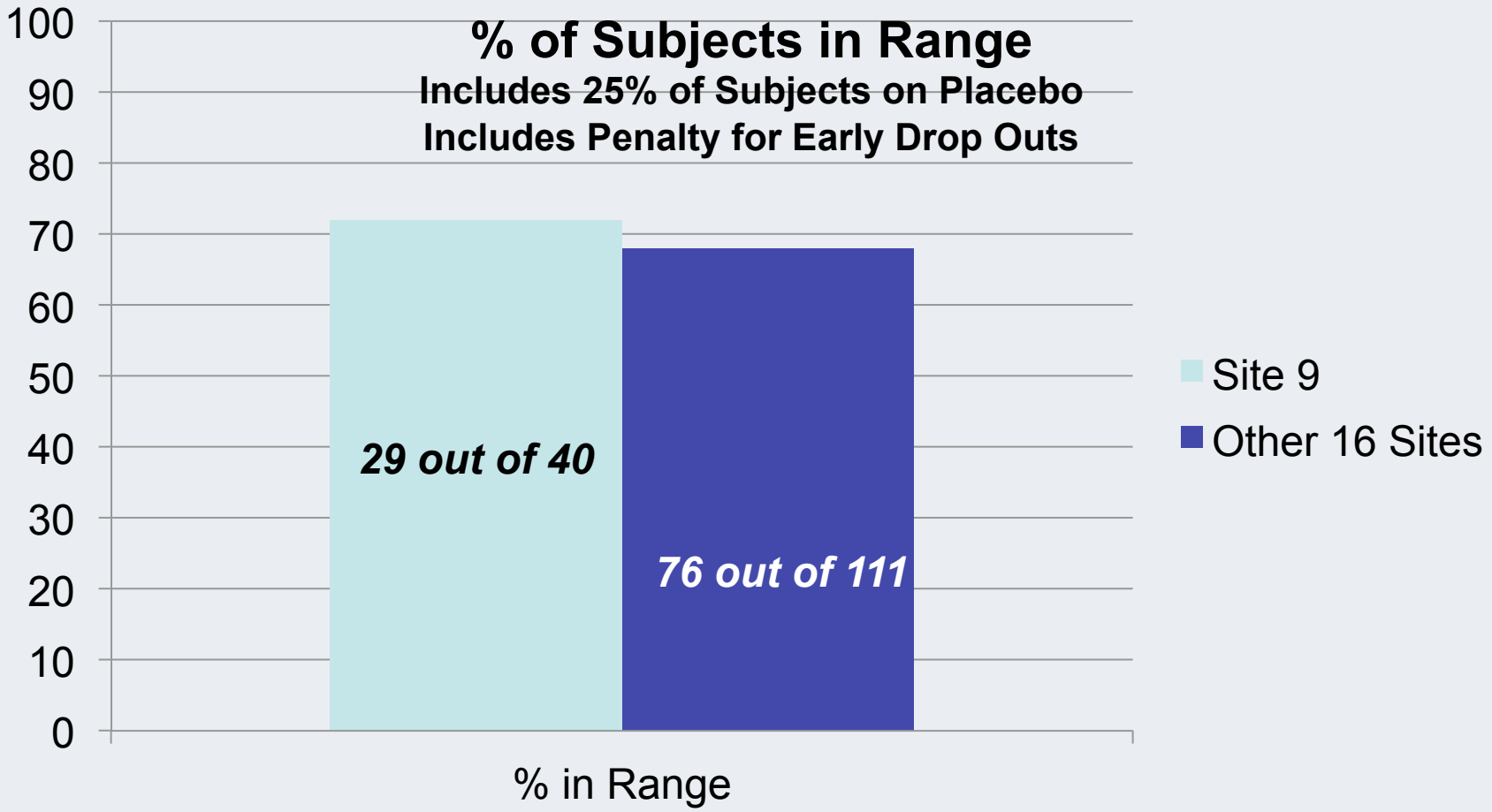
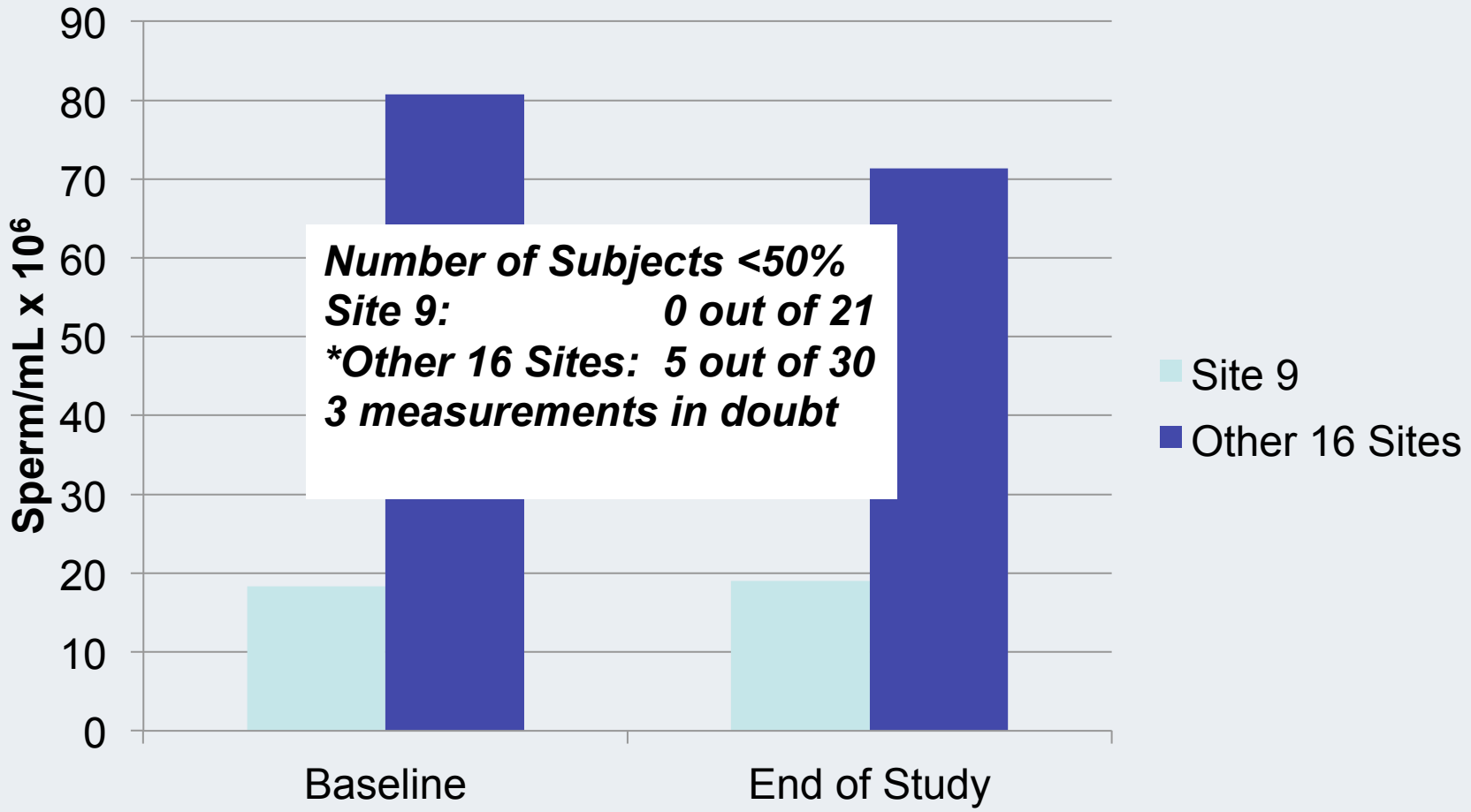


Drop outs before Week 6
Site 9: 3 out of 40
Others: 2 out of 111

ZA-301 Testosterone Endpoint



Blinded Mean Sperm Counts Subjects Completing Study



Number of Subjects <50%
Site 9: 0 out of 21
****Other 16 Sites: 5 out of 30***
3 measurements in doubt