T6015

EVALUATION OF RESIDUAL LEVONORGESTREL AS POTENTIAL BIOEQUIVALENCE METRIC FOR A LONG ACTING INTRAUTERINE SYSTEM USING QUANTITATIVE MODELING AND SIMULATION APPROACH

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2017 AAPS ANNUAL MEETING & EXPOSITION

PURPOSE

A long acting intrauterine system (IUS) containing levonorgestrel (LNG) is indicated for contraception up to 5 years and for treatment of heavy menstrual bleeding for women who choose to use IUS as their method of contraception. It contains 52 mg of LNG and it is intended to provide an initial release rate of about 20 mcg/day which is reduced by about 50 % after 5 years. Because of its local delivery of LNG, a conventional pharmacokinetic (PK)-based bioequivalence (BE) approach may play a lesser role in assessing the therapeutic equivalence of LNG IUS. In addition, considering that this product is designed to deliver LNG up to 5 years, a clinical endpoint BE study lasting for 5 years may not be practically feasible. Accordingly, we explored alternative BE study designs that involve product physicochemical characterizations and a short term BE study. We assessed BE metrics and statistical criteria, using quantitative modeling and simulation approaches, for the alternative in vivo BE approaches for generic LNG IUS.

METHODS

Residual LNG was evaluated as alternative BE metric. Observed residual LNG data were retrieved from the LNG IUS drug applications submitted to the Agency. A first order rate equation (Residual LNG = $A \times e^{-kt}$, where A is the constant representing LNG content (mg) in the system at time zero and k is first order rate constant (day^{-1})) explained the observed data with incorporated variability. Then hypothetical LNG IUS generic products with various different population release rate constants ranging from plus 100 percent to minus 100 percent from the reference release rate constant were generated. Subsequently, a virtual parallel BE study was conducted to compare the reference product and hypothetical generic products at different time points. We used Berkeley Madonna (version 8.3.23.0) and R (version 3.3.1) software for the analysis.

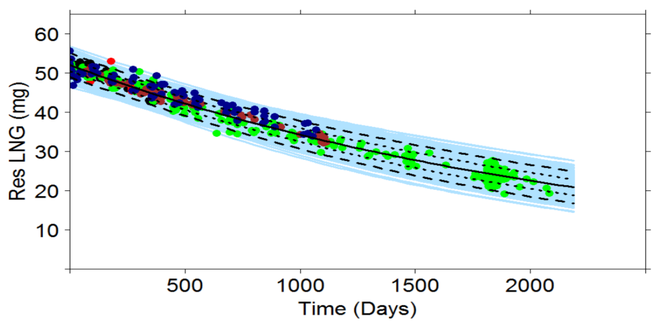

Figure 1: Observed Residual LNG from Virtual Population (n = 1000) and from an array of Investigational New Drug (IND) and New Drug Applications (NDA) with study durations of 1, 3, and 5 years.

RESULTS

Table 1: Parallel BE Study Results at 1 Year and 5 Year for Hypothetical Generics with Faster Release.

		$\mu_R + \delta\mu_R$	
δ (%)		Year 1	Year 5
0 (0%)	GMR (Lower, Upper)	100.00 (98.47, 101.56)	100.03 (95.90, 104.35)
0.05 (5%)	GMR (Lower, Upper)	99.25 (97.72, 100.80)	96.33 (92.26, 100.58)
0.1 (10%)	GMR (Lower, Upper)	98.50 (96.97, 100.05)	92.74 (88.73, 96.92)
0.2 (20%)	GMR (Lower, Upper)	97.02 (95.49, 98.58)	86.00 (82.11, 90.07)
0.4 (40%)	GMR (Lower, Upper)	94.14 (92.61, 95.70)	73.97 (70.32, 77.81)
0.6 (60%)	GMR (Lower, Upper)	91.34 (89.80, 92.90)	63.59 (60.17, 67.20)
0.8 (80%)	GMR (Lower, Upper)	88.61 (87.06, 90.18)	54.64 (51.46, 58.02)
1.0 (100%)	GMR (Lower, Upper)	85.97 (84.41, 87.56)	46.98 (44.02, 50.14)

Table 2: Parallel BE Study Results at 1 Year and 5 Year for Hypothetical Generics with Slower Release.

		$\mu_R - \delta\mu_R$	
δ (%)		Year 1	Year 5
0 (0%)	GMR (Lower, Upper)	100.00 (98.46, 101.55)	100.01 (95.87, 104.32)
0.05 (5%)	GMR (Lower, Upper)	100.76 (99.23, 102.31)	103.87 (99.67, 108.25)
0.1 (10%)	GMR (Lower, Upper)	101.53 (100.00, 103.08)	107.89 (103.62, 112.33)
0.2 (20%)	GMR (Lower, Upper)	103.06 (101.52, 104.62)	116.29 (111.88, 120.87)
0.4 (40%)	GMR (Lower, Upper)	106.24 (104.69, 107.82)	135.39 (130.65, 140.31)
0.6 (60%)	GMR (Lower, Upper)	109.50 (107.92, 111.10)	157.44 (152.26, 162.79)
0.8 (80%)	GMR (Lower, Upper)	112.86 (111.24, 114.49)	183.10 (177.32, 189.07)
1.0 (100%)	GMR (Lower, Upper)	116.32 (114.67, 118.00)	213.00 (206.37, 219.86)

- Hypothetical generic products (TEST) with release rate constants differing by 5% up to 100% (δ) as compared to Reference Listed Drug (RLD) were generated (i.e. $\mu_R \pm \delta \times \mu_R$).
- BE analysis was performed on residual LNG from virtual subjects (n = 20) for RLD and hypothetical generics using 80% - 125% BE limit.
- Then 90% confidence interval of geometric mean ratio (GMR) of the RLD and TEST at 1 year and 5 years were computed and the procedure was repeated 1000 times simulating 1000 studies.

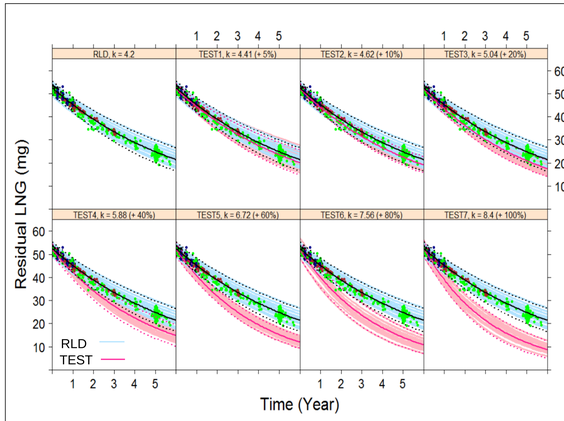

Figure 2: Observed Residual LNG from Different Formulations and Model Simulated Residual LNG in Virtual Population with Hypothetical Generic Formulations.

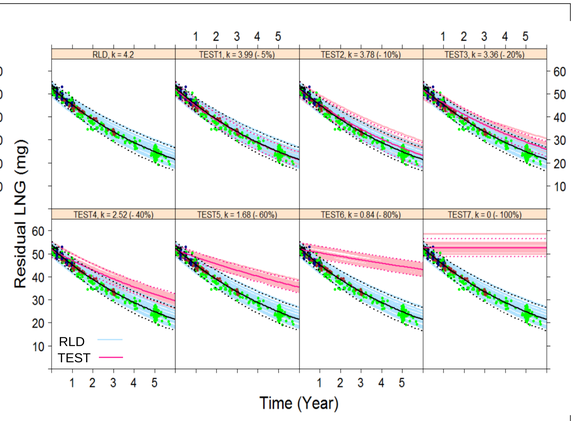

Figure 3: Observed Residual LNG from Different Formulations and Model Simulated Residual LNG in Virtual Population with Hypothetical Generic Formulations.

RESULTS

- Assuming that BE limits at 5 years are 80% and 125%, the number of studies passing the BE limits at 1 year and 5 years can be computed for different BE limits at 1 year varying from 93% – 100/0.93% to 97% – 100/0.97%.
- If the proposed BE limit is appropriate, the chance of passing the BE criteria at 1 year is expected to be similar to the chance of passing the BE criteria at 5 years.

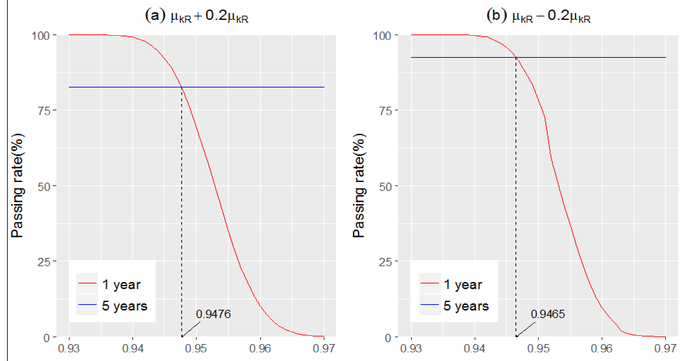

Figure 4: BE Limit of 95 – 105.26 % for Residual LNG at 1 year can be proposed to ensure BE limit of 80 – 125 at 5 year.

- Proposed BE limit of 95 – 105.26 % for Residual LNG at 1 year was evaluated by retrieving the residual LNG data for formulation C (which is also marketed in Europe and Asia) and formulation D (marketed in US)..
- BE analysis with proposed BE limit of 95 – 105.26 % at 1 year showed that the formulation C and D were bioequivalent.
- A one year in vivo BE study would significantly shorten product development time and could potentially encourage generic competition in the LNG IUS product category.

CONCLUSION

- Residual LNG, which directly relates to the absolute amount of LNG delivered while inserted, was evaluated as a potential metric for BE determination of LNG IUS.
- Our analysis suggests that a BE limit of 95-105.26% for residual LNG at one-year (12 M post insertion) would ensure that residual LNG amount at five year is within 80 – 125 %.

DISCLAIMER

The views presented in this poster by the authors do not necessarily reflect those of the Food and Drug Administration (FDA).