Exposure-Response Analysis of AZD4901 in Women with Polycystic Ovary Syndrome in a Phase IIa Study
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Purpose
AZD4901 (formerly AZD2624, originally studied for schizophrenia) is a Neurokinin 3 (NK3) receptor antagonist. It is hypothesized that AZD4901 could reduce the secretion of luteinizing hormone (LH), and thus decrease testosterone in women with polycystic ovary syndrome (PCOS). A randomized, placebo-controlled Phase IIa study of AZD4901 effects on LH and testosterone in women with PCOS was conducted (1). The objective of this analysis was to perform exposure-response analysis of AZD4901 to evaluate the pharmacokinetic/pharmacodynamic relationship of AZD4901 and LH or testosterone.

Methods
This analysis dataset included sixty-one PCOS patients who were randomly assigned to 1 of the following 4 treatments: 20 mg AZD4901 once daily (QD), 20 mg AZD4901 twice daily (BID), 40 mg AZD4901 twice daily, or placebo. Investigational product was administered orally beginning on Day 1 and continuing through the morning of Day 28. On Days -1, 7, and 28, multiple samples for the analyses of LH (every 10 minutes) and testosterone (hourly) profiles were collected from prior to dosing until 8 hours following the morning dose. AZD4901 AUC₀⁻⁸ on day 7 and day 28 was obtained by non-compartmental analysis. LH pulse frequency was derived using blinded deconvolution analysis (2), a validated methodology conducted by Dr. Johannes Veldhuis (Mayo Clinic). The PKPD relationship between AZD4901 dose or individual AUC₀⁻⁸ and LH AUC₀⁻⁸, average total testosterone concentration in 8 hours (TT Cavg), or LH pulse frequency (number of pulses in 8 hours) on day 7 and day 28 were first explored by graphical visualization. The PD endpoints were analyzed as change from baseline (day 7 vs. day -1 or day 28 vs. day -1). The exposure-response analysis was performed using linear mixed effects modeling in R (nlme package).

Results
The geometric mean (CV%) of AZD4901 AUC₀⁻⁸ after 20 mg QD, 20 mg BID and 40 mg BID were 1500 (37%), 2310 (33%), 4190 (32%) ng/mL*h for day 7 and 1610 (31%), 2400 (30%) and 3730 (21%) ng/mL*h for day 28, respectively. This suggests AZD4901 has reached steady state by day 7. LH and total testosterone decreased at day 7 and were sustained to day 28 in majority of patients in highest dose group (40 mg twice daily). Graphical exploration with loess curve indicated a clear dose-response relationship on all three endpoints (LH AUC₀⁻⁸ CFB, TT Cavg CFB and LH pulse frequency CFB) on day 7, but was not obvious on day 28. The relationship was stronger between AZD4901 AUC₀⁻⁸ and PD endpoints compared to dose vs. PD endpoints. The linear mixed effects modeling of AZD4901 AUC₀⁻⁸ with LH AUC₀⁻⁸ CFB on day 7 revealed a significant correlation with a mean coefficient of -4.0 [90% confidence interval (CI): -7.8, -0.25] IU/L*h per 1000 ng/mL*h. The coefficient on day 28 was not statistically significant at -2.6 [90% CI: -7.2, 2.0] IU/L*h per 1000 ng/mL*h. AZD4901 AUC₀⁻⁸ with TT Cavg CFB and LH pulse frequency CFB modeling resulted in significant linear exposure-response relationships on both day 7 and day 28. The mean coefficients were -0.094 and -0.063 nmol/L per 1000 ng/mL*h on day 7 and day 28 for TT Cavg CFB and -0.76 and -0.40 pulses per 1000 ng/mL*h on day 7 and day 28 for LH pulse frequency CFB, respectively.

Conclusion
The linear mixed effects modeling of AZD4901 AUC₀⁻⁸ and LH AUC₀⁻⁸, TT Cavg and LH pulse frequency suggest there is a significant exposure-response linear relationship. The developed models can be used to predict response at different dose regimens in similar settings in future clinical development.

References