P-19.
Q-1001: A Phase 1b Study of the Safety and Effect of Q-122 on Vasomotor Symptoms in Females with Breast Cancer
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Objective: QUE Oncology is developing Q-122, a novel, orally available small molecule with the chemical formula N-(4-(pyrimidin-2-ylamino)methyl)benzyl)-pyrimidin-2-amine, as a treatment for vasomotor symptoms (VMS) commonly associated with menopause. The initial target population for the development program is females with a history of breast cancer who are taking tamoxifen or an aromatase inhibitor (AI). The first proof of concept study in this population was Q-1001, a Phase 1b, open-label, two dose, dose-escalation study evaluating the safety, tolerability and preliminary effectiveness of Q-122 therapy. Design: Study Overview: Q-1001 was a single-site study that enrolled female subjects who were menopausal, age 30 – 70 years, with a history of breast cancer and taking tamoxifen or an AI. To be eligible for the study, subjects had to be experiencing at least 7 moderate to severe hot flashes (HF) per day or 50 per week. Key exclusion criteria included significant renal or hepatic disease, untreated hyperthyroidism and clinically significant abnormal laboratory findings. Although paroxetine is approved for treatment of moderate to severe VMS, concurrent therapy with SSRIs or SNRIs was not an exclusion criterion. The study period consisted of a 2-week drug free screening period to establish baseline values of VMS, a 4-week treatment period, and a final 2-week drug-free follow-up period before the final study termination visit. Subjects were initially enrolled into Group 1 (100 mg Q-122). After Group 1 was fully enrolled, safety parameters were reviewed prior to enrolling subjects into Group 2 (200 mg Q-122). Methods: Safety was monitored by reporting of adverse events (AEs) and serious adverse events (SAEs), and evaluation of treatment emergent adverse changes in physical findings and laboratory values. Efficacy was assessed by calculating the mean changes in frequency and severity of moderate to severe HF from baseline to Week 4. For comparison across treatment weeks, a daily average frequency of HF was calculated for each treatment week. Severity was assessed by calculating a HF severity score (HFSS) that was normalized to frequency for each treatment week. Results: Twenty-one subjects received Q-122 of which 20 were included in the efficacy analysis; 8 subjects in each group completed the study. Safety: A total of 29 AEs with one SAE were reported during the study (10 in 7 of 10 subjects in Grp. 1; 19 (including 1 SAE) in 7 of 11 subjects in Grp. 2). All the reported AEs were mild (79%) or moderate (21%) in severity. Three AEs reported by one subject (headaches (2 events), and insomnia) were the only events considered possibly related to study drug by the Investigator. There were no remarkable or dose-related changes in adverse events, physical findings or laboratory values. Efficacy: After 4 weeks of treatment with Q-122, both frequency and normalized severity of moderate to severe HF were significantly reduced from baseline values. The reduction was seen in each dose group, in all subjects combined, and in subjects who were taking an SSRI or SNRI. Baseline (BSLN) and Change from Baseline (CFB) in moderate and severe HF frequency and severity is displayed in Table 1. Conclusion: No safety issues associated with the use of Q-122 were identified in this study. Further, Q-122 therapy resulted in reduction in both frequency and severity of VMS over the 4-week treatment period. These results compare favorably with published results from studies assessing the ability of other non-hormonal drugs to treat VMS in various populations.

Table 1: Change in Frequency and Severity of Moderate to Severe Hot Flashes Following Treatment with Q-122

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grp 1 (N=9)</th>
<th>Grp 2 (N=11)</th>
<th>All (N=20)</th>
<th>S/SN-RI (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (daily average)</td>
<td>BSLN 8.86</td>
<td>8.58</td>
<td>9.16</td>
<td>8.11</td>
</tr>
<tr>
<td></td>
<td>CFB -5.81</td>
<td>-5.6</td>
<td>-5.69</td>
<td>-5.07</td>
</tr>
<tr>
<td>HFSS (normalized to freq.)</td>
<td>BSLN 2.48</td>
<td>2.41</td>
<td>2.44</td>
<td>2.54</td>
</tr>
<tr>
<td></td>
<td>CFB -0.47</td>
<td>-0.38</td>
<td>-0.42</td>
<td>-1.21</td>
</tr>
</tbody>
</table>
Relationship between Equol Producer Status and Metabolic Parameters in 743 Healthy Women

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Objective: Equol is an active metabolite produced by the action of intestinal flora on soy isoflavones and possesses the estrogen-like actions. It could be produced naturally from the consumption of soybean isoflavones in about 50% of Japanese female population. There is increasing evidence on its efficacy in the relief of menopausal symptoms, suppression of decreased bone mineral density, improving lipid profiles, and decreasing the risk for breast and prostate cancer. This study aimed to examine the relationship between equol producer status and the parameters related to lifestyle related diseases in women in their twenties to eighties.

Design: This cross-sectional study was conducted among 743 healthy women (21 – 89 years; average age: 52.5 ± 11.8 years) who have undergone health screening at Tokyo Midtown Medical Center and given consent to participate in the study. The equol production status was defined by detection of urinary equol more than 1.0 μM. The metabolic parameters include anthropometric measures, lipid profiles and atherosclerosis related biomarkers. The relationship between equol production status and parameters were assessed using Mann-Whitney test and associations were further confirmed on logistic regression analysis.

Results: In our study 236 women (32%) are equol producers. Equol producer proportion is the highest in women in their twenties (n =18, 39%), lowest in women in their eighties (n=9, 22%), and the proportions in the remaining age populations are 32% (30’s: n=79), 31% (40’s: n=222), 31% (50’s: n=214), 32% (60’s: n=121), 37% (70’s: n=78). Overall, there is no significant difference in BMI, blood pressure, lipid profile (triglycerides, HDL cholesterol), HbA1c and bone mineral density between producer and non-producers of equol. However, when stratified by age, women in their fifties who are equol producers show significantly lower body fat level (25.7 ± 6.4 V.S. 27.8 ± 6.8, p<0.5), visceral fat CT scan (41.8 ± 20.0 V.S. 54.0 ± 26.8 cm, p<0.01), PWV (1289 ± 89 V.S. 1375 ± 251 cm/s, p<0.05). In addition, homocysteine levels tend to be lower in women in their sixties who are producers of equol (7.9 ± 1.8 V.S. 8.8 ± 2.2, p=0.068). In multivariate logistic regression, increased EPA/AA ratio was significantly associated with higher odds for equol producer status (AOR= 6.778, 95% CI: 1.431 – 32.098, p<0.05) whereas elevated uric acid and pulse wave velocity were associated with lower odds (AOR=0.660, 95% CI: 0.452 - 0.962, p=0.05 and AOR: 0.998, CI: 0.996 – 1.000, p=0.05 respectively) in women in their fifties. On the other hand, equol producers are less likely to be associated with high homocysteine (AOR: 0.736, 95% CI: 0.546 – 0.992, p<0.05) and urinary NTx (AOR: 0.967, 95% CI: 0.940 - 0.994, p<0.05) levels in women in their sixties.

Conclusion: Equol producer status is associated with favorable metabolic parameters, especially anti-atherosclerotic conditions, in women of postmenopausal age. This study provides additional literature on the examination of the relationship between equol and lifestyle related risk factors among postmenopausal women with declining intrinsic estrogen. Based on these preliminary results, future research should test the influence of equol producer status on these parameters, including the assessment of daily consumption habits of soy and other phytoestrogen compounds, smoking habit, omega-3 supplement consumption and current medication for dyslipidemia or osteoporosis.
Lasofoxifene, an estrogen agonist/antagonist improves symptoms of genitourinary syndrome of menopause (GSM) and physiologic markers associated with vulvovaginal atrophy (VVA) in two large Phase 3 studies

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Objective: Many women suffer from genitourinary symptoms in menopause as a consequence of falling sex steroid levels. A significant number remain untreated due to fears of estrogen-containing products and inconvenience of local vaginal administration. Lasofoxifene is an estrogen agonist-antagonist, or SERM, demonstrating beneficial effects on bone density, fracture risk and breast cancer risk in menopausal women in large randomized trials out to five years. Herein, results of 2 phase 3 randomized, placebo controlled studies for the treatment of VVA are presented.

Design: Two identical 12 week randomized placebo-controlled Phase 3 treatment studies evaluated lasofoxifene 0.25mg and 0.5mg oral tablets per day vs placebo using 4 co-primary endpoints (measured as change from baseline to week 12) for the treatment of moderate to severe symptoms of VVA: change in pH, percentage of superficial cells, percentage of parabasal cells, and patient self-assessed most- bothersome symptom (MBS). Women had to have at least one moderate to severe symptom of vaginal dryness, dyspareunia, vaginal/vulvar itching, dysuria and a pH of <5 and percent superficial cells <5%. 889 women age 50-80 were randomized and 810 (91%) completed 12 weeks of treatment. Women were allowed to use non-hormonal lubricant as needed during the trial. Changes from baseline in coprimary endpoints were analyzed using analysis of covariance (ANCOVA).

Results: VVA efficacy measurements were collected at 2, 4, 8 and 12 weeks with primary efficacy assessed at 12 weeks. Treatment groups were similar with respect to mean baseline measures for the co-primary endpoints. Average subject age was 59. The moderate to severe baseline symptom most commonly chosen as most bothersome was dyspareunia, followed by vaginal dryness, dysuria, and vulvar and vaginal itching. The adjusted mean decreases in MBS were 1.4 in both lasofoxifene treatment groups, compared with a decrease of 1.0 in the placebo group, where a score of 0 corresponds to absence of the symptom, and a score of 3 corresponds to a rating of “severe.” Both comparisons between lasofoxifene treatment groups and placebo were statistically significant with p-values <0.00001. A greater decrease in vaginal pH was reported in both lasofoxifene treatment groups relative to placebo-treated subjects at 12 weeks of treatment in the pooled analysis. The adjusted mean decreases in pH were 0.81 and 0.83 in the lasofoxifene treatment groups compared with a decrease of 0.20 in the placebo group. Comparisons between lasofoxifene treatment groups and placebo were statistically significant with p-values <0.00001. A greater mean decrease in the percentage of vaginal parabasal cells was observed in both lasofoxifene treatment groups relative to placebo-treated subjects at 12 weeks of treatment in the pooled analysis. The adjusted mean decreases were 40.1% and 40.4% in both lasofoxifene treatment groups compared with a decrease of 6.2% in the placebo group. Both comparisons between a lasofoxifene treatment group and placebo were statistically significant with p-values <0.00001. The mean increases in superficial cells were 6.5% and 5.9% in both lasofoxifene treatment groups compared with an increase of 2.1% in the placebo group in the pooled analysis. Both comparisons between a lasofoxifene treatment group and placebo were statistically significant with p-values <0.00001. Results of all pooled analyses for all the co-primary endpoints were similar to those of the individual studies. The most common side effects occurring in the treatment group were vaginal discharge, hot flashes and leg cramps. Conclusion: Lasofoxifene 0.25mg and 0.5mg daily, in each of the individual and pooled studies, demonstrated a statistically and clinically meaningful improvement in the 4 co-primary endpoints, with several demonstrating beneficial effect as early as 2 weeks. Lasofoxifene is an effective and well-tolerated treatment of moderate to severe symptoms of VVA and offers women an alternative to vaginal and oral estrogens that provide a meaningful benefit for the relief of bothersome symptoms of GSM/VVA while conferring extra-genital benefits to bone and breast health.
DXA assessment of adiposity is a better predictor of metabolic risk than BMI

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Objective: There is a well known epidemic of obesity in the United States. It is a major factor in developing cardiometabolic abnormalities, although weight alone allows somewhat imprecise prediction. Body Mass Index (BMI) developed almost 175 years ago as a measure of relative weight based on an individual’s mass and height is expressed by WHO definitions, arbitrarily derived, as “normal weight, overweight, and obese.” BMI is neither age nor gender specific. Previously, we presented data on a cohort of postmenopausal women where percent body fat was measured by dual x-ray absorptiometry (DXA) and converted into percentiles for age and gender. Approximately 20% of normal weight women were greater than the 75th percentile for total body fat (deemed “skinny fat”) while 20% of overweight women were between 25-75th percentile. All obese women were above the 75th percentile while 20% of normal weight women were less than the 25th percentile (lean). This is not dissimilar to the work of Wildman et al that found that there are groups of individuals with metabolic dysfunction despite a lean prototype and healthy obese people who are protected from metabolic dysfunction. They assessed a cross sectional sample of 5440 participants in the National Health and Nutrition Examination Surveys (NHANES) 1999-2004, for cardiometabolic abnormalities including weight, blood pressure, C-reactive protein, fasting glucose, insulin resistance and serum lipids. They found that 23.5% of normal weight adults were metabolically abnormal, while 51.3% of overweight adults and 31.7% of obese adults were metabolically healthy. It has been established, however, that android or truncal adipose tissue distribution compared to gynoid (hips and buttocks) has a greater association with metabolic dysfunction. Thus, obesity related complications are less associated with fat mass per se than the distribution of that fat. Dual X-ray Absorptiometry (DXA) uses small amounts of x-ray to produce a total body image. The x-ray is composed of two energy levels that are absorbed differently by bone, lean and fat tissues. These differences are used to determine the amount of lean and fat tissues across the whole body. Realizing that location of body fat may be more relevant than total body fat, special software can measure visceral adipose tissue (VAT) expressed either in pounds or volume. Traditional DXA yields percent body fat in the android region and gynecoid region, yielding an A/G ratio. This study was undertaken 1) to see the correlation between A/G ratio and VAT and 2) the correlation between BMI and VAT. Design: 113 postmenopausal women who had a routine DXA scan for bone mass indication and who had whole body scans for body composition were collected retrospectively and consecutively. GE Lunar Core Scan© software (GE, Milwaukee, WI.) was utilized. A/G ratio as well as VAT in pounds and volume were obtained. This was then compared to their BMI calculated by measuring their height and weight. Statistical analysis of the correlation was carried out using Spearman’s nonparametric correlation coefficient test because of the non-normality of data. Two sided p-values <0.05 were considered to be statistically significant. Statistical analysis was performed using R (www.R-project.org). Results: Correlation between VAT in pounds and volume was rho=0.9999. The correlation between VAT and A/G ratio was rho=0.82 for both fat mass in pounds and fat volume. In addition, correlation between percent body fat in the android region and VAT in either pounds or volume was also rho=0.82. However, the correlation between BMI and VAT (either pounds or volume) was rho=0.45. Conclusion: This underscores the notion that BMI, while commonly employed in standard medical practice, does not correlate well with VAT, a well recognized risk factor for developing cardiometabolic abnormalities. Furthermore, the correlation between standard A/G ratio or even just percent fat in the android region on DXA, compared with VAT produced with newer proprietary software, is sufficiently strong to continue to use standard A/G ratio as a surrogate for visceral adiposity, although, further prospective study is necessary to see its actual correlation with cardiometabolic parameters.