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THE USE OF COGNITIVE FUNCTION TESTING TO IDENTIFY POTENTIAL COGNITION ENHANCERS IN PHASE I: CASE HISTORIES OF TRANSITIONAL MEDICINE. S. T. Satek; K. A. Wesnes; Cognitive Drug Research, Ltd., Chicago, IL, United Kingdom

BACKGROUND: Drugs under development as cognition enhancers can be evaluated in Phase I for potential efficacy using tests of cognitive function. Case studies will be presented showing the utility of such evaluation in identifying potential candidates for subsequent development.

METHODS: The Cognitive Drug Research (CDR) computerized assessment system has been widely used in worldwide Phase I research and has an extensive bibliography for identifying cognitive enhancements in volunteers and various patient populations. It assesses core domains of function including attention, information processing, working memory and episodic memory. The individual tests are brief, fully automated and can be repeatedly administered over hours, days or weeks. This enables the testing to be seamlessly incorporated into safety and tolerability Phase I trials without compromising the primary objectives of such work. Its use in such studies, as well as pharmacodynamic models (scopolamine model of dementia, sleep deprivation model) will be described.

RESULTS: Three case histories will be provided showing how the inclusion of testing in safety trials accurately predicted subsequent efficacy in Alzheimer’s disease (AD) patients with S-12024, Adult ADHD with NS2359 and Age-Associated Memory Impairment and Mild Cognitive Impairment with TCI734/AZD3480. In the scopolamine model, ZT-1 showed comparable utility to donepezil, and has since been found effective in AD. Finally, modafinil was found to be effective in reversing sleep deprivation induced cognitive deficits in volunteers, and subsequent work has shown the r-isomer to be highly effective in narcolepsy and shift work sleep disorder.

CONCLUSION: Cognitive testing in Phase I with an appropriately sensitive and validated tests can provide information which is predictive to patients, and thus satisfies the requirements for being a practical, appropriate, valid and sensitive technique in translational medicine.

PIII-47

EFFECT OF AROMATASE INHIBITORS, LETROZOLE AND EXEMESTANE, ON PLATELET COUNT AND AGGREGATION IN WOMEN WITH BREAST CANCER. J. Miao, Y. Kreutz, A. T. Nguyen, S. M. Lemler, Z. Desta, D. A. Flockhart, Y. Jin; West China Hospital, Sichuan University, Chengdu, P.R. China; The division of clinical pharmacology of IUPUI, Indianapolis, IN

BACKGROUND: Increased cardiovascular risk is of clinical concern during chronic treatment with aromatase inhibitors in postmenopausal women with breast cancer. We tested whether aromatase inhibitors influence platelet count and aggregation.

METHODS: Postmenopausal women with estrogen receptor positive breast cancer were randomized to receive letrozole (2.5 mg/day) or exemestane (25mg/day). Blood samples were collect before and 3 months after initiating treatment. Platelet counts were measured using a COULTER® Advanced Platelet Analyzer. Platelet aggregation was assessed by light transmission aggregometry after stimulation with adenosine diphosphate (ADP), arachidonic acid (AA), and collagen. Polymorphisms in ER genes: ESR1-03 (ERα PvuII), ESR1-39 (ERα XbaI) and ESR2-02 were determined by TaqMan® Assays. EAR1 haplotype was estimated using the PHASE II.

RESULTS: Four common haplotypes [T-A (47.9%), C-G (34.8%), C-A (15.9%), T-G (1.0%)] were observed based on the ESR1-03 and ESR1-39 genotypes in 67 patients. While mean platelet count decreased in the entire cohort, this increase was most evident in women who carried 1 or none T-A allele (21.62±59.98x106/pL, P<0.01), or in subjects who carried at least a C-G allele (24.54±57.14x10^6/pL, P=0.01). ESR2-02 were not associated with changes in platelet counts. Associations between ESR genotype and changes in platelet aggregations were evaluated in subjects who used consistently cyclooxygenase-1 inhibitors (n=47). No associations between polymorphisms in either ESR genes and changes in platelet aggregation were observed.

CONCLUSION: ESR1 genetic polymorphisms may influence aromatase inhibitor-induced increases in platelet count and may alter the cardiovascular risk of these medications in selected patients as a result.

PIII-48

ASSOCIATION OF ESTROGEN RECEPTOR HAPLOTYPE WITH AROMATASE INHIBITOR-INDUCED PLATELET CHANGES. J. Miao, Y. Kreutz, A. T. Nguyen, S. M. Lemler, Z. Desta, D. A. Flockhart, Y. Jin; West China Hospital, Sichuan University, Chengdu, P.R. China; The division of clinical pharmacology of IUPUI, Indianapolis, IN

BACKGROUND: Estrogen regulates platelet function via platelet estrogen receptors. Therefore, depletion of estrogen by aromatase inhibitors may increase cardiovascular risk. We tested the hypothesis that polymorphisms in estrogen receptor genes may influence platelet function after aromatase inhibitor treatment.

METHODS: Postmenopausal women with estrogen receptor(ER) positive breast cancer were randomized to receive exemestane (25mg/day) or letrozole (2.5 mg/day). Blood samples were collect before and 3 months after initiating treatment. Platelet counts were measured using a COULTER® Advanced Platelet Analyzer. Platelet aggregation was assessed by light transmission aggregometry after stimulation with adenosine diphosphate (ADP), arachidonic acid (AA), and collagen. Polymorphisms in ER genes: ESR1-03 (ERα PvuII), ESR1-39 (ERα XbaI) and ESR2-02 were determined by TaqMan® Assays. EAR1 haplotype was estimated using the PHASE II.

RESULTS: Three case histories will be provided showing how the inclusion of testing in safety trials accurately predicted subsequent efficacy in Alzheimer’s disease (AD) patients with S-12024, Adult ADHD with NS2359 and Age-Associated Memory Impairment and Mild Cognitive Impairment with TCI734/AZD3480. In the scopolamine model, ZT-1 showed comparable utility to donepezil, and has since been found effective in AD. Finally, modafinil was found to be effective in reversing sleep deprivation induced cognitive deficits in volunteers, and subsequent work has shown the r-isomer to be highly effective in narcolepsy and shift work sleep disorder.

CONCLUSION: Cognitive testing in Phase I with an appropriately sensitive and validated tests can provide information which is predictive to patients, and thus satisfies the requirements for being a practical, appropriate, valid and sensitive technique in translational medicine.

PIII-49

INCLUSION OF SUBPOPULATIONS IN EARLY PHASE CLINICAL TRIALS SUBMITTED TO THE FDA: A REVIEW OF NMES APPROVED IN 2006. E. Pinnow, A. Parekh, P. Sharma, N. Gevorkian, K. Uhl; FDA, Rockville, MD

BACKGROUND: Historically subpopulations such as women & the elderly have been excluded from clinical trials. This is particularly evident in Phase 1 trials. The goal of this study was to determine the overall participation of women & elderly subjects in Phase 1 trials & the dose ranges studied in these populations.

METHODS: Clinical trials submitted to the FDA for New Molecular Entities (NMEs) for adult, non-sex specific indications in 2006 the first 3 month. In the remaining 47 patients, no statistically significant changes were observed in ADP, AA and collagen induced aggregation before and after aromatase inhibitors treatment.

CONCLUSION: Aromatase inhibitor treatment lead to an increase in platelet count without any significant change in platelet aggregation.
were reviewed. Electronic data available on Phase 1 studies were evaluated for proposed indications, sex & age of participants & doses tested. Therapeutic doses were obtained from the approved labeling.

RESULTS: FDA approved 18 NMEs for non-sex-specific indications in 2006. Data for 194 Phase I studies of 16 NMEs were reviewed, 1 was not available electronically & 1 provided only summary demographic data. Overall 29.5% (183/6231) of study participants were women, 3.6% were ≥65, 95/194 (49.0%) studies included safety/tolerability testing above the highest approved dose. In trials that included a dose above the highest recommended dose, 31.4% of participants were women, 3.6% were elderly. 65 (33.5%) trials were exclusively male & 129 (66.5%) also enrolled females. 21 (10.8%) enrolled participants ≥ age 65. Similar percentages of studies, overall & those including a dose above the highest recommended dose, included women & elderly participants.

CONCLUSION: Women & elderly subjects are underrepresented in Phase 1 trials. In early phase dose escalation safety/tolerability trials where drug exposure exceeds the highest therapeutic dose, the importance of including women and elderly subjects should be considered, because of potential differences in response and as they will be exposed postmarketing.

<table>
<thead>
<tr>
<th>Number and Percent of Trials Including Female and Elderly Participants</th>
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</thead>
<tbody>
<tr>
<td><strong>Trials including female participants</strong></td>
</tr>
<tr>
<td>All Trials (n=194) tested</td>
</tr>
<tr>
<td>129 (66.5%)</td>
</tr>
<tr>
<td>64 (67.4%)</td>
</tr>
<tr>
<td>21 (10.8%)</td>
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<td>10 (10.5%)</td>
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PIII-50

BACKGROUND: Identification and analysis of the dose and response relationships in clinical trials is central to the assessment of safety and efficacy in clinical trials. The observation of a strong positive correlation between dose and outcome is commonly viewed as evidence supporting a causal relationship. This report describes the situation where highly significant correlations between dose and outcome do not represent true dose-response relationships.

METHODS: The dose response relationships for test drug (HBOC-201), a hemoglobin-based oxygen carrier, and control therapy, transfusion with packed red blood cells (RBC), were examined in two single blind, randomized and controlled phase III clinical trials (Hem-0115 and Hem-0114) investigating the treatment of acute surgical anemia in the perioperative elective surgical setting. Patients were randomized to treatment with HBOC-201 (N=350) or RBC (N=338 or 77) and the extent of blood avoidance and safety were evaluated in studies Hem-0115 and Hem-0114, respectively.

RESULTS: Regression analysis using a simple general linear model revealed a significant correlation between dose of HBOC-201 and the extent of blood avoidance and safety measured in terms of the number of adverse events per patient (AE/pt) in study Hem-0115: AE/pt = 5.25±0.61 + 0.77±0.12[HBOC]. p< 0.0001. A similar relationship for dose of control treatment: AE/pt = 3.43±0.48 + 0.81±0.13[RBC] with p< 0.0001. As confirmation, highly significant (p< 0.0001) correlations for HBOC-201: AE/pt = 4.8±0.48 + 0.78±0.13[HBOC] and dose of RBC: AE/pt = 2.57±0.94 + 0.83±0.16[RBC] were observed in study Hem-0114.

CONCLUSION: Randomization of drug therapy to dose is preferable but not always possible and when not, dose response relationships can be confounded which predisposes to misinterpretation. The accuracy of the assessment will be greatest in the situation where dose is determined by clinical need and clinical need is the primary predictor of risk (AE/pt).