August, the 1st, 2017, Lodz,

**EXPLANATION OF REQUEST FOR PROPOSALS ZO-07-2017**

TO ALL INTERESTED PARTIES

By following point 10 of Chapter VI, the ordering party informs that within the request for proposals pre-clinical tests (physiochemical, ADME-tox, genotoxicity, safety pharmacology and toxicological tests) necessary to commence 1st phase clinical trials for EC313., conducted in the mode of inquiry based on the provisions of the Act of April 23, 1964 - the Civil Code (Journal of Laws 2014, item 212, as amended), **questions were recieved**. Please find the questions and answers are **below**:

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***Question 1:*** Is there a reason you are not going to be running a 4 week study? Our scientific advisor has indicated that going from a DRF with a 7 day dosing phase to a 13 week study is risky. There is a risk of running into unexpected toxicity once you get past 7 days with the worst case scenario that doses do not make it for 13 weeks. In addition for a primate study the questions from IACUC would be around dose level justification based on a DRF for a 13 week study and the level of comfort that you wouldn’t see excessive toxicity.  
  
Answer: The R&D toxicology program is based on prior drug development experience as it pertains to hormonal steroids. These type of drug candidates when on the market have demonstrated to be highly tolerated. Therefore, there is no need to run a 4-week toxicology study since even after 13 weeks it is anticipated that no serious adverse effects will be observed.   
  
  
***Queistion 2***: Analytical (formulation and bioanalysis).  The package contains a mix of non-GLP and GLP studies.  We would recommend that we quote for performing GLP method development and validation of the assays for formulations and sample bioanalysis for use on both the non-GLP and GLP studies.  This will save you money rather than running non-GLP and also non-GLP methods.  Please let me know if this is acceptable.  
  
Answer:  The contracting party kindly informs that aforementioned is acceptable.  
  
  
***Queistion 3***:  Given the indication do you want everything in female animals only?  Typically companies would include both genders in case they find a new indication for the test article, but other times they limit it based on the indication they are currently looking at.  If it is females only for all studies, then some of the following would be impacted.

Answer: The choice of female animals is based on the indication in woman’s health (endometriosis)  
  
***Question 4***: No mention of TK in the rat DRF study (but there is in the NHP), we would recommend including in the rat study.

Answer: The TK is not required in DRF study.

***Question 5***: It appears you want some kind of forms analysis in the DRFs (mention stability etc) but that is not required for non-GLP studies.

Answer: The contracting party explains that these tests should be performed prior to the DRF test, but in such a standard that they can be used for a 13-week study.

***Question 6***: For the rat DRF, not sure how the design would look if the total number of animals is 25, hopefully that should be 25/sex?  Our standard design, if we don’t include TK and only have three arms in Phase A would be 29/sex.

Answer: The amount of animals is indicative. If the Contractor sees the need to use more animals - this is acceptable, but should explain the rationale in "comments". However one should bear in mind that this study is to be performed on females only.

***Question 7***: Can you provide any information about the animals, since that could be an issue for us depending on where they are coming from.  In addition can you confirm you are be able to ship them to the US?

Answer: The contracting party clarifies the following: In the case in which the contracting entity supplies laboratory animals, the tenderer should state the requirements for the animals in the Comments column for each task / study (wherever applicable). The contracting party can deliver them to US location, if required.

***Question 8***: For the 13 week rat you indicate for the TK groups it would only be treated, but that is not GLP compliant – you need TK for the control group as well.  You indicate a total of 80 animals, but that would only cover the main study, does not include recovery (please confirm which groups are to go to recovery) and does not include TK (which would be 3/sex for control and 6/sex for treated, plus extras).

Answer: The amount of animals is indicative for main study. If the bidder sees the need to use more animals - this is acceptable, but the animals should be only females and any additional number of animals should be describe it in the column "comments”. Therefore the contracting party confirms that main, recovery and TK groups should be included.