05 June 2018

Dear Sirs and Madams,

Also referring to our letter of March 03, 2017, we would like to inform you that medac has decided to early terminate the clinical study MC-TER.2/SSc (TERGISS). The study has been temporarily halted in March 2017 prior to the clinical start of study MC-TER.2/SSc (TERGISS). Although the study has been approved by the competent authorities and received positive opinions from the ethics committees, study sites have not been initiated yet and no patients have been enrolled.

Some unforeseen results of a Phase 1 study (MC-TER.3/PK) conducted in 2016 led medac to further investigate questions on the optimal dose titration schedule and the safety of terguride in a new phase 1 study (MC-TER.4/PK), and to halt TERGISS until the results of the study MC-TER.4/PK are available.

Study MC-TER.3/PK showed that the metabolism of terguride is strongly dependent on the hepatic CYP2D6 pathway with AUC and C_{max} varying considerably among the predicted phenotype groups, resulting in substantial inter-individual variability in tolerability and cardiovascular events (i.e. tachycardia up to 10 beats/min in poor and intermediate metabolizers for CYP2D6). The consequences for dose titration were evaluated in the additional phase I multiple dose study MC-TER.4/PK, focusing on cardiovascular parameters in the various metabolic groups during up titration.

Study MC-TER.4/PK confirmed a clinically relevant increase of heart rate as well as of systemic and diastolic blood pressure in healthy subjects who are poor or intermediate metabolizers in which high exposures of terguride were reached. These findings were not observed in the extensive and ultra-rapid metabolizers.

Based on these results further in-depth studies are required and thus, medac has decided not to recommence the TERGISS study.

Best regards,

Cécile Guimbal-Schmolck
Clinical Scientific Program Lead
c.guimbal-schmolck@medac.de
+49 4103 8006 434

Renate von der Weth
Project Manager TERGISS
r.weth@medac.de
+49 4103 8006 8324

Perry De Jongh
Head of Clinical Research
P.deJongh@medac.de
+49 4103 8006 738