Transferability of ETP-based APC resistance assay on the ST Genesia system

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Clotting

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BACKGROUND

- Regulatory bodies recommend assessing the ETP-based APC resistance assay during the development of steroid contraceptives.
- In 2019, this assay was validated on the Calibrated Automated Thrombogram using commercially available reagents to ensure batch-to-batch traceability, and reproducibility of the method over time.

AIMS

To implement the ETP-based APC resistance assay on the automated ST Genesia system using reagent STG-ThromboScreen -TM (TS –TM) with exogenous APC added.

METHODS

- Determination of APC concentration leading to 90%±2.5% of ETP inhibition of a healthy pooled plasma, using 2 different batches of TS –TM.
- Intra- (N=5) and inter-run (N=10) reproducibility of ETP inhibition assessed on 3 lyophilized samples.
- Reference ranges defined based on 56 plasma samples.
- Sensitivity assessed on 36 females using combined oral contraceptives (COCs).

RESULTS

- $[APC]_{mU/mL}$ defined at 652 mU/mL [IC95%: 534-805 mU/mL] on both batches of TS – TM (**Figure 1**).
- ETP inhibition SD <2.0% for intra-run and <3.5% for inter-run reproducibility (**Table 1**).
- Mean ETP inhibition % [IC95] over 56 samples equaled 89.5% [87.3%-91.6%] (**Figure 2**).
- Significantly lesser response to APC of women using COC compared to healthy individuals (**Figure 2**).

SUMMARY/CONCLUSION

This study is the first reporting the transferability of the ETP-based APC resistance assay on the ST Genesia system. Data revealed excellent precision (within- and between-run reproducibility) and provided an appropriate sensitivity depending on the hormonal status of women. Confirmation of promising results on thrombogenicity identification for all COC users is still needed before this test can be commercially available.

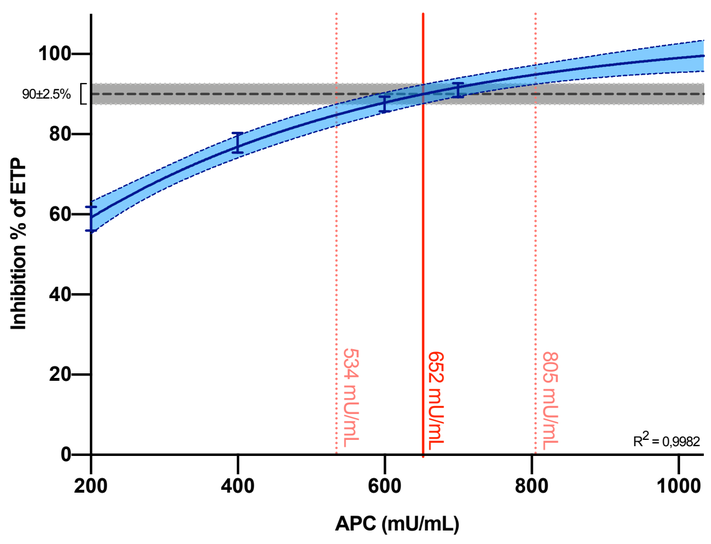

Figure 1: Inhibition percentages of ETP of a healthy pooled plasma (HPP) at various concentrations of APC (mU/mL), using two batches of TS –TM. The blue continuous line represents the mean non-linear regression obtained with both batches of TS –TM. The horizontal grey dotted lines represent the maximal tolerated inhibition percentage of HPP, corresponding to 90% ±2.5% . The red vertical lines represent the APC concentration [IC95] leading to 90% of inhibition of the ETP and corresponds to 652 mU/mL [534-805 mU/mL].

Tested plasma	ETP inhibition reproducibility	
	Intra-run (N=5) Mean ± SD	Inter-run (N=10) Mean ± SD
STG-RefPlasma TS	73.5% ± 1.0%	74.5% ± 3.5%
STG-QualiTest Norm TS	38.5% ± 2.0%	37.7% ± 3.5%
STG-QualiTest High TS	8.7% ± 1.7%	10.1% ± 1.4%

Table 1: Intra-run and inter-run reproducibility of ETP inhibition of the commercial reference plasma and two quality controls.
Intra-run reproducibility was based on 5 measurements of each tested plasma and the inter-run reproducibility was based on 10 runs measuring each tested plasma.
Results are expressed as mean inhibition % ± standard deviation (SD)

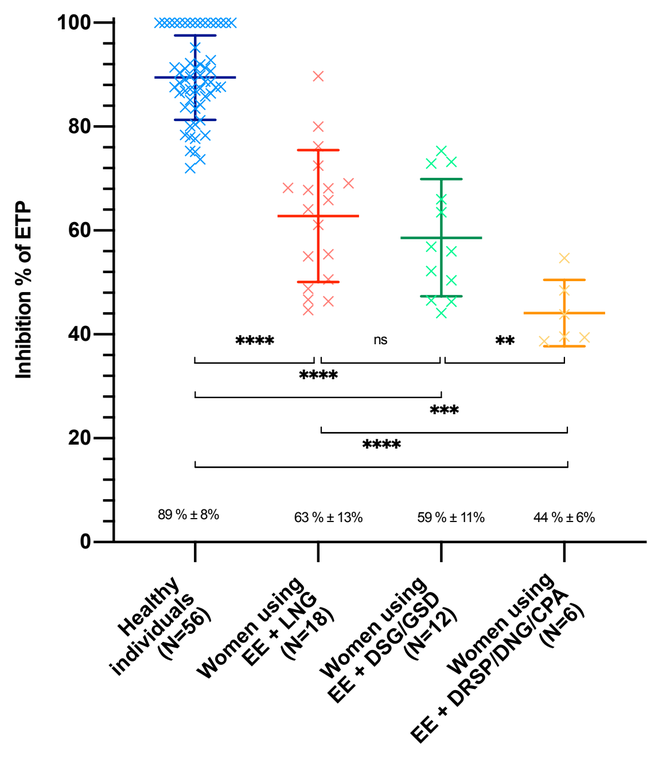

Figure 2: Inhibition % of ETP of individuals from each subgroup, i.e., healthy individuals (N=56), women using COC containing:
- ethinylestradiol (EE) + levonorgestrel(LNG) (N=18);
- EE + desogestrel (DSG)/ gestodene(GSD) (N=12);
- EE + drospirenone (DRSP)/ cyproterone acetate (CPA)/ dienogest (DNG) (N=6).

Individuals values and mean ETP inhibition ± SD for each subgroup are represented. Differences between subgroups were assessed by a Holm-Sidak's multiple comparison test. P-value are characterized as following: ns = P>0.05; * = P≤0.05; ** = P≤0.01 ; *** = P ≤0.001; **** = P ≤0.0001

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