



## Clinical Study Synopsis for Public Disclosure

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<b>Title of trial:</b>	An open-label, two-period, fixed-sequence trial to evaluate the effect of multiple doses of BI 10773 on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in healthy premenopausal female volunteers																											
<b>Principal Investigator:</b>	[REDACTED]																											
<b>Trial site:</b>	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany																											
<b>Publication (reference):</b>	Data of this study have not been published.																											
<b>Clinical phase:</b>	I																											
<b>Objectives:</b>	The objective of this study was to investigate the possible effect of multiple oral doses of 25 mg empagliflozin (BI 10773) on the steady state pharmacokinetics of ethinylestradiol and levonorgestrel (Microgynon®).																											
<b>Methodology:</b>	This was an open-label, 2-period, fixed-sequence study.  After a run-in period of 28 to 55 days (treatment with Microgynon® once daily [q.d.] for 21 to 48 days, depending on menstrual cycle, followed by a tablet-free interval of 7 days), subjects began the first (reference) treatment period of Microgynon® alone for 14 days, immediately followed by the second (test) treatment period of Microgynon® plus empagliflozin for 7 days.																											
<b>No. of subjects:</b>	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;"><b>planned:</b></td> <td colspan="3" style="padding: 2px;">Entered: 18</td> </tr> <tr> <td style="padding: 2px;"><b>actual:</b></td> <td colspan="3" style="padding: 2px;">Entered: 18</td> </tr> <tr> <td style="padding: 2px;"></td> <td colspan="3" style="padding: 2px;">Reference treatment: 1 tablet Microgynon® once daily (q.d.) for 14 days</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px;">Entered: 18</td> <td style="padding: 2px;">treated: 18</td> <td style="padding: 2px;">analysed (for primary endpoint): 18</td> </tr> <tr> <td style="padding: 2px;"></td> <td colspan="3" style="padding: 2px;">Test treatment: 1 tablet Microgynon® q.d. + 25 mg empagliflozin q.d. for 7 days</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px;">Entered: 18</td> <td style="padding: 2px;">treated: 18</td> <td style="padding: 2px;">analysed (for primary endpoint): 18</td> </tr> </table>				<b>planned:</b>	Entered: 18			<b>actual:</b>	Entered: 18				Reference treatment: 1 tablet Microgynon® once daily (q.d.) for 14 days				Entered: 18	treated: 18	analysed (for primary endpoint): 18		Test treatment: 1 tablet Microgynon® q.d. + 25 mg empagliflozin q.d. for 7 days				Entered: 18	treated: 18	analysed (for primary endpoint): 18
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<b>Diagnosis and main criteria for inclusion:</b>	Healthy premenopausal female subjects age 18 to 39 years with a body mass index of 18.5 to 27 kg/m <sup>2</sup> and no relevant gynaecological findings were eligible for this trial.																											

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<b>Trial product 1:</b>	Empagliflozin film-coated tablet			
<b>dose:</b>	25 mg			
<b>mode of admin.:</b>	Oral			
<b>batch no.:</b>	909473A			
<b>Trial product 2:</b>	Microgynon <sup>®</sup> coated tablet			
<b>dose:</b>	30 µg ethinylestradiol + 150 µg levonorgestrel			
<b>mode of admin.:</b>	Oral			
<b>batch no.:</b>	91955B, 93842C			
<b>Duration of treatment:</b>	Run-in period (Microgynon <sup>®</sup> ): 21 to 48 days, depending on menstrual cycle Reference treatment (Microgynon <sup>®</sup> ): 14 days Test treatment (Microgynon <sup>®</sup> + empagliflozin): 7 days			
<b>Criteria for evaluation:</b>	<p><b>Pharmacokinetics:</b> The relative bioavailabilities of ethinylestradiol and levonorgestrel at steady state were investigated based on the primary endpoints <math>AUC_{\tau,ss}</math> and <math>C_{max,ss}</math> of each analyte.</p> <p>The secondary pharmacokinetic (PK) endpoints were the <math>t_{max,ss}</math>, <math>MRT_{po,ss}</math>, <math>V_z/F_{ss}</math>, <math>CL/F_{ss}</math>, <math>\lambda_{z,ss}</math>, and <math>t_{1/2,ss}</math> of ethinylestradiol and levonorgestrel.</p> <p>Pre-dose plasma concentrations of empagliflozin, ethinylestradiol, and levonorgestrel were measured to determine attainment of steady state.</p> <p><b>Safety:</b> Safety and tolerability were evaluated based on adverse events, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (haematology, coagulation, clinical chemistry, and urinalysis), and assessment of tolerability by the investigator.</p>			

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<b>Statistical methods:</b> <p>The relative bioavailabilities of ethinylestradiol and levonorgestrel were estimated using analysis of variance with factors treatment (fixed effect) and subject (random effect) on log-transformed parameters to calculate the geometric mean ratio and 90% confidence intervals of <math>AUC_{\tau,ss}</math> and <math>C_{max,ss}</math> between the test and reference treatments.</p> <p>Descriptive statistics were calculated for all PK endpoints.</p> <p>The safety analysis comprised frequency tabulations and descriptive statistics.</p>				
<b>SUMMARY – CONCLUSIONS:</b> <p><b>Trial subjects:</b> The treated set comprised 18 healthy female subjects. All subjects completed the trial according to the protocol. No important protocol violations or deviations from the inclusion or exclusion criteria were reported.</p> <p>The mean (minimum to maximum) age and body mass index of the subjects were 27.2 (20 to 37) years and 22.62 (19.4 to 26.0) kg/m<sup>2</sup>. No concomitant diagnoses at baseline were reported and no concomitant therapies were considered relevant.</p> <p>After a run-in period of Microgynon<sup>®</sup> q.d. for 21 to 48 days followed by a tablet-free interval of 7 days, 18 subjects received Microgynon<sup>®</sup> q.d. for 14 days followed by Microgynon<sup>®</sup> q.d. and 25 mg empagliflozin q.d. for 7 days.</p> <p><b>Pharmacokinetics results:</b> Steady state concentrations of both ethinylestradiol and levonorgestrel were reached by Day 12 of the reference treatment (Microgynon<sup>®</sup>) and steady state concentrations of empagliflozin were reached by Day 5 of the test treatment (Microgynon<sup>®</sup> and empagliflozin).</p> <p>When Microgynon<sup>®</sup> was given with and without empagliflozin, the mean <math>AUC_{\tau,ss}</math> of ethinylestradiol was 956 vs 932 pg·h/mL and the mean <math>C_{max,ss}</math> was 99 pg/mL in both treatments; the mean <math>AUC_{\tau,ss}</math> of levonorgestrel was 102 vs 99.6 ng·h/mL and the mean <math>C_{max,ss}</math> was 8.71 vs 8.24 ng/mL. The plasma concentration-time profiles and other PK parameters of both ethinylestradiol and levonorgestrel were similar in both treatments.</p>				

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<b>Pharmacokinetics results (continued):</b>	<p>The geometric mean ratios (90% confidence intervals) of <math>AUC_{\tau,ss}</math> and <math>C_{max,ss}</math> of ethinylestradiol when Microgynon<sup>®</sup> was given with and without empagliflozin were 102.82% (97.58%, 108.35%) and 99.22% (93.40%, 105.39%), respectively. The corresponding values for levonorgestrel were 101.94% (98.54%, 105.47%) and 105.81% (99.47%, 112.55%). Thus, the 90% confidence intervals were within the standard bioequivalence boundaries of 80.00% to 125.00%. Intra-individual variability in all comparisons was low.</p>			
<b>Safety results:</b>	<p>Treatment-emergent adverse events were reported in a total of 16 subjects – 10 subjects during treatment with Microgynon<sup>®</sup> alone and 10 subjects during treatment with Microgynon<sup>®</sup> and empagliflozin. The most frequently reported adverse event was headache, reported in 4 subjects (3 subjects during treatment with Microgynon<sup>®</sup> and 1 subject during treatment with Microgynon<sup>®</sup> and empagliflozin).</p> <p>No serious adverse events or adverse events leading to discontinuation of the trial medication were reported.</p> <p>Adverse events which the investigator considered related to the study medication were reported in a total of 5 subjects – 2 subjects during treatment with Microgynon<sup>®</sup> alone (dizziness and nausea) and 3 subjects during treatment with Microgynon<sup>®</sup> and empagliflozin (dizziness, nausea, and thirst).</p> <p>Severe adverse events, all of which were headache, were reported in 4 subjects. The investigator did not consider any severe headaches drug-related.</p> <p>At the end of each treatment, the investigator assessed global tolerability as 'good' in 17 subjects and 'satisfactory' in 1 subject.</p>			
<b>Conclusions:</b>	<p>Co-administration of empagliflozin with Microgynon<sup>®</sup> had no effect on the pharmacokinetics of ethinylestradiol or levonorgestrel with respect to the standard bioequivalence boundaries of 80.00% to 125.00%. The combination of empagliflozin and Microgynon<sup>®</sup> was well tolerated. These results demonstrate that empagliflozin does not affect the pharmacokinetics of ethinylestradiol or levonorgestrel and no dosage adjustment of ethinylestradiol or levonorgestrel is required when these medications are concomitantly administered with empagliflozin.</p>			

**Trial Synopsis - Appendix**

The results table on the following page supplements the trial results presented in the Trial Synopsis. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

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<b>Results for</b>	<b>presented in</b>
Pharmacokinetic parameters of ethinylestradiol after multiple oral administration of 1 tablet Microgynon alone or 1 tablet Microgynon + 1 tablet empagliflozin (25 mg)	Table 15.6.3: 1

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Table 15.6.3: 1 Comparison of pharmacokinetic parameters of ethinylestradiol after multiple oral administration of Microgynon tab (30 ug EE/150 ug LNG), qd alone or in combination with 25 mg empagliflozin tab, qd

	N	Microgynon tab (30 ug ethinylestradiol/ 150 ug levonorgestrel)				N	25 mg empagliflozin tab with Microgynon tab (30 ug ethinylestradiol/ 150 ug levonorgestrel)			
		gMean	gCV [%]	Mean	CV [%]		gMean	gCV [%]	Mean	CV [%]
AUC <sub>t,ss</sub> [pg*h/mL]	18	907	24.4	932	24.4	18	932	22.8	956	24.2
C <sub>max,ss</sub> [pg/mL]	18	97.6	17.6	99.0	17.0	18	96.8	21.8	99.0	22.1
t <sub>max,ss</sub> [h]	18	1.37	39.5	1.48	44.6	18	1.68	34.2	1.78	40.1
λ <sub>z,ss</sub> [1/h]	18	0.0454	28.8	0.0469	24.8	18	0.0425	21.8	0.0434	21.7
t <sub>½,ss</sub> [h]	18	15.3	28.8	15.9	32.4	18	16.3	21.8	16.7	21.7
MRT <sub>po,ss</sub> [h]	18	18.6	28.1	19.3	30.9	18	19.5	20.5	19.8	19.9
CL/F <sub>t,ss</sub> [mL/min]	18	552	24.4	567	23.5	18	536	22.8	549	20.8
V <sub>z/F,ss</sub> [L]	18	729	35.1	769	32.5	18	757	30.3	788	27.5