Novel AKR1C3 inhibitor affects androgen metabolism but not ovarian function in healthy women: A phase 1 study.

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1 Methods

1.1 In-vitro assay for IC50 for inhibition of human AKR1C3 enzyme

Biochemical enzyme assay

Human AKR1C3 (aldo-keto reductase family 1 member C3, Gene ID: 8644) was expressed in Escherichia coli (E. coli) as glutathione S transferase (GST) fusion protein and purified by glutathione sepharose affinity chromatography. The GST was removed by digestion with thrombin. Enzyme activity was measured by quantification of coumberol formation from coumberone, a metabolic fluorogenic substrate for AKR1C3 (5, 6), at a coumberone concentration of 0.3 µmol/L (Km). The fluorescence of coumberol was then measured, and the intensity of the fluorescence was used as a measure of coumberol amount formed and thus of AKR1C3 enzyme activity. IC_{50} values were calculated using a 4-parameter fit.

1.2 Pharmacokinetic evaluation

1.2.1 Bioanalytical methods

The concentrations of BAY1128688 and its metabolite BAY1107202 (M-7) in plasma were determined after protein precipitation with acetonitrile including an internal standard and 0.1% acetic acid followed by separation employing high-pressure liquid chromatography– tandem mass spectrometry (LC-MS/MS). Method validation and analyses of study samples were performed in compliance with the relevant guidelines of the US Food and Drug Administration. Quality control samples were included in each analytical run (performance parameters in Suppl. Table 1).

1.2.2 Pharmacokinetic methods

The following non-compartmental single- and multiple-dose PK parameters were determined for the parent drug BAY1128688 and its metabolite BAY1107202 (M-7) using the software WinNonlin v5.3 (Certara, Princeton, NJ):

- the area under the plasma concentration–time curve from time zero to infinity after single-dose administration (AUC);
- the area under the plasma concentration–time curve from time zero to 24 h post-dose after single-dose and multiple-dose administration (AUC(0-24), $AUC(0\text{-}24)_{multiple\text{-}dose}$);
- the maximum observed concentration in plasma after single-dose and multiple-dose administration (C_{max}, $C_{max,multiple\text{-}dose}$);
- the minimum observed concentration in plasma after multiple-dose administration ($C_{min,multiple\text{-}dose}$);
- the time to maximum concentration (t_{max}, $t_{max,multiple\text{-}dose}$); and
- the half-life associated with the terminal slope (t½).

Based on these parameters, dose-normalized area under the plasma concentration–time curve and C_{max} values, the metabolic ratio MR ($MR = (AUC(0\text{-}24)_{metabolite}/AUC(0\text{-}24)_{parent}) \times (molecular\ weight_{parent}/molecular\ weight_{metabolite})$), the accumulation ratio R_AAUC ($R_AAUC = AUC(0\text{-}24)_{multiple\text{-}dose}/AUC(0\text{-}24)$), and the linearity index R_{LIN} ($R_{LIN} = AUC(0\text{-}24)_{multiple\text{-}dose}/AUC$) were determined.

1.2.3 Population pharmacokinetic and pharmacokinetic/-dynamic modeling methods

A population pharmacokinetic (popPK) model and a population pharmacokinetic/pharmacodynamic (popPK/PD) model were developed to describe the plasma concentrations of BAY1128688 and the time-course of bilirubin in serum, respectively. The models were developed based on data from the present study and on data from the first-in-human study with BAY1128688, a single-dose escalation study in healthy postmenopausal women (Bayer; data on file). PopPK and popPK/PD analyses were performed via

non-linear mixed-effects modeling methods applied in NONMEM v7.3 (ICON Development Solutions, Dublin, Ireland).

1.3 Evaluation of exploratory biomarkers for renal safety

To detect early signs of drug mediated kidney damage, the following clinically qualified markers were determined in 24-hour urine samples using technically validated methods:

- kidney injury molecule 1 (KIM-1);
- neutrophil gelatinase-associated lipocalin;
- albumin,
- cystatin C; and
- creatinine.

This evaluation was conducted in *post*menopausal women (Part A).

2 Results

2.1 Supplemental tables

Suppl. Table 1: Performance of the LC-MS/MS method for the quantification of BAY1128688 and BAY1107202 in plasma

	Analyte	
Quality parameter	**BAY1128688**	**BAY1107202**
Calibration range	1.00 (LLOQ) to 1000 µg/L (ULOQ)	1.00 (LLOQ) to 1000 µg/L (ULOQ)
Calibration standards mean inter-assay accuracy of back-calculated concentrations (except LLOQ)	99.0% to 102.0%	98.6% and 101.0%
Calibration standards precision (except LLOQ)	≤ 5.6%.	≤ 5.1%.
Accuracy at the lowest calibration standard (LLOQ)	101.0%	100.0%
Precision at the lowest calibration standard (LLOQ)	6.9%,	5.1%,
Concentration range of QC samples	3.00 to 850 µg/L	3.00 to 850 µg/L
QC samples accuracy	98.4% to 100.0%	96.8% to 99.0%
QC samples precision	4.8% to 5.8%.	3.7% to 6.0%.

LC-MS/MS, liquid chromatography–tandem mass spectrometry; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Suppl. Table 2: Serum concentrations [nmol/L] of 17 steroids in *post*menopausal women before, during, and after 14-day administration of BAY1128688

		Placebo				3 mg QD				30 mg QD				60 mg BID				90 mg QD		
Analyte (LLOQ)	**Day**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
11-Deoxycortisol	-0	7	0.49	0.28	1.26	5	0.59	0.45	0.79	7	0.44	0.14	0.92	7	0.41	0.23	1.08	7	0.46	0.17	2.01
(0.014)	1	7	0.35	0.24	1.13	5	0.38	0.19	0.50	7	0.31	0.18	1.18	7	0.56	0.17	1.30	7	0.47	0.20	1.04
	6	7	0.58	0.21	1.42	5	0.37	0.18	0.96	7	0.24	0.14	0.86	7	0.34	0.16	0.75	7	0.44	0.17	0.82
	13	7	0.48	0.23	0.70	5	0.42	0.17	0.66	7	0.38	0.15	0.66	7	0.46	0.12	0.75	7	0.28	0.14	0.39
	14	7	0.50	0.43	1.38	5	0.33	0.15	0.84	7	0.35	0.14	1.03	7	0.50	0.28	0.72	7	0.33	0.13	0.82
	15	7	0.49	0.25	0.98	5	0.38	0.16	0.79	7	0.42	0.13	1.30	7	0.40	0.21	0.71	7	0.40	0.16	0.53
	19	7	0.35	0.25	0.74	5	0.20	0.15	0.80	7	0.33	0.14	0.71	7	0.38	0.23	0.72	7	0.30	0.20	0.54
11-Deoxycorticosterone	-0	7	0.082	0.042	0.168	5	0.085	0.075	0.095	7	0.042	0.017	0.103	7	0.056	0.030	0.126	7	0.062	0.035	0.176
(0.023)	1	7	0.068	0.034	0.152	5	0.074	0.045	0.090	7	0.051	0.022	0.143	7	0.076	0.028	0.183	7	0.052	0.032	0.116
	6	7	0.089	0.027	0.235	5	0.083	0.047	0.109	7	0.036	0.017	0.128	7	0.077	0.020	0.102	7	0.058	0.043	0.100
	13	7	0.075	0.032	0.088	5	0.059	0.042	0.079	7	0.042	0.021	0.074	7	0.061	0.018	0.106	7	0.038	0.025	0.070
	14	7	0.081	0.048	0.179	5	0.057	0.031	0.106	7	0.046	0.015	0.112	7	0.066	0.034	0.097	7	0.050	0.019	0.105
	15	7	0.059	0.036	0.103	5	0.062	0.033	0.111	7	0.061	0.019	0.132	7	0.080	0.031	0.116	7	0.049	0.027	0.086
	19	7	0.071	0.046	0.085	5	0.057	0.041	0.097	7	0.049	0.023	0.080	7	0.070	0.038	0.105	7	0.060	0.029	0.076
17α-Hydroxyprogesterone	-0	7	0.52	0.22	0.64	5	0.53	0.37	0.61	7	0.35	0.17	0.52	7	0.44	0.34	0.94	7	0.38	0.20	0.89
(0.038)	1	7	0.44	0.30	0.65	5	0.38	0.24	0.50	7	0.33	0.23	1.03	7	0.45	0.29	0.94	7	0.47	0.21	0.80
	6	7	0.48	0.34	0.83	5	0.39	0.23	0.50	7	0.27	0.15	0.66	7	0.41	0.25	0.59	7	0.45	0.18	0.80
	13	7	0.40	0.31	0.54	5	0.29	0.23	0.58	7	0.33	0.18	0.46	7	0.33	0.18	0.70	7	0.28	0.15	0.52
	14	7	0.65	0.47	0.91	5	0.30	0.19	0.64	7	0.30	0.15	0.56	7	0.43	0.30	0.64	7	0.28	0.17	1.01
	15	7	0.45	0.29	0.53	5	0.30	0.21	0.56	7	0.37	0.17	0.94	7	0.43	0.30	0.66	7	0.30	0.16	0.61
	19	7	0.46	0.24	0.56	5	0.33	0.22	0.44	7	0.30	0.18	0.79	7	0.45	0.27	0.56	7	0.34	0.18	0.57
Aldosterone	-0	7	0.095	0.060	0.120	5	0.120	0.067	0.325	7	0.079	0.027	0.192	6	0.091	0.055	0.118	5	0.108	0.033	0.187
(0.139)	1	7	0.082	0.028	0.171	4	0.131	0.097	0.286	7	0.073	0.033	0.163	7	0.110	0.057	0.184	6	0.155	0.060	0.220
	6	7	0.087	0.041	0.172	5	0.306	0.065	0.663	7	0.132	0.071	0.411	7	0.098	0.050	0.228	6	0.095	0.075	0.201
	13	7	0.067	0.036	0.116	4	0.137	0.088	0.152	7	0.060	0.052	0.131	7	0.092	0.059	0.149	6	0.060	0.030	0.122
	14	7	0.070	0.057	0.251	4	0.162	0.122	0.333	7	0.070	0.050	0.113	7	0.088	0.071	0.179	6	0.089	0.055	0.136
	15	7	0.084	0.071	0.264	4	0.181	0.102	0.424	7	0.139	0.045	0.265	7	0.165	0.029	0.277	7	0.126	0.033	0.217
	19	7	0.078	0.039	0.158	4	0.225	0.060	0.266	7	0.096	0.061	0.358	7	0.098	0.044	0.164	6	0.088	0.059	0.208

		Placebo				3 mg QD				30 mg QD				60 mg BID				90 mg QD		
Analyte (LLOQ)	**Day**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
Androstenedione	-0	7	1.05	0.89	1.82	5	1.45	1.33	2.20	7	1.21	0.94	2.06	7	1.38	0.93	2.06	7	1.24	1.04	1.82
(0.028)	1	7	1.10	0.68	1.74	5	1.32	0.86	1.91	7	1.43	0.94	2.09	7	1.47	1.02	2.20	7	1.29	1.02	1.79
	6	7	1.32	0.79	2.04	5	1.69	0.93	2.65	7	1.40	0.71	1.99	7	1.19	0.77	1.93	7	1.30	0.80	2.33
	13	7	1.00	0.81	1.93	5	1.17	0.90	2.16	7	1.14	0.95	1.66	7	1.18	0.62	2.09	7	0.96	0.81	1.41
	14	7	1.75	0.87	2.79	5	1.67	0.87	1.93	7	1.30	1.00	2.15	7	1.47	0.86	2.63	7	1.06	0.90	1.54
	15	7	1.12	0.65	2.84	5	1.09	0.91	2.44	7	1.22	0.80	2.77	7	1.53	0.81	2.42	7	1.08	0.86	1.64
	19	7	0.92	0.74	1.78	5	1.04	0.73	2.06	7	1.24	0.88	1.63	7	1.30	0.93	1.70	7	1.15	0.79	1.56
Androsterone	-0	5	0.15	0.05	0.27	5	0.26	0.16	0.49	7	0.23	0.12	0.57	6	0.18	0.09	0.22	6	0.21	0.11	0.24
(0.104)	1	5	0.11	0.02	0.27	3	0.32	0.28	0.47	7	0.31	0.10	0.82	7	0.38	0.12	0.42	7	0.35	0.17	0.76
	6	6	0.15	0.11	0.19	5	0.25	0.16	0.47	7	0.48	0.22	1.06	7	0.60	0.31	0.79	7	0.81	0.22	0.94
	13	5	0.18	0.12	0.23	5	0.30	0.16	0.50	7	0.34	0.21	1.25	7	0.49	0.24	1.07	7	0.62	0.11	1.16
	14	6	0.19	0.08	0.25	5	0.29	0.14	0.46	7	0.47	0.24	1.00	7	0.58	0.19	1.22	7	0.74	0.35	0.95
	15	6	0.14	0.08	0.23	5	0.24	0.15	0.48	7	0.25	0.13	0.73	7	0.49	0.16	0.73	6	0.57	0.25	0.75
	19	7	0.13	0.09	0.18	5	0.18	0.11	0.42	7	0.22	0.08	0.59	5	0.26	0.14	0.31	6	0.24	0.10	0.35
Corticosterone	-0	7	12.2	5.1	14.7	5	13.7	9.4	17.5	7	8.3	3.0	17.2	7	11.5	4.4	23.8	7	7.8	3.7	24.7
(0.022)	1	7	8.0	3.0	15.0	5	5.7	3.5	8.8	7	5.1	2.1	21.8	7	13.7	2.9	27.8	7	5.9	3.9	12.9
	6	7	6.7	3.8	24.1	5	6.4	5.0	12.0	7	5.2	2.3	19.3	7	10.9	2.4	16.8	7	7.6	2.9	11.2
	13	7	8.9	3.6	19.8	5	6.3	5.2	14.5	7	5.5	2.4	11.2	7	15.2	2.6	20.2	7	4.4	3.4	7.9
	14	7	12.0	6.7	34.0	5	6.0	3.9	21.7	7	4.5	2.5	15.5	7	14.1	5.9	18.1	7	7.8	1.4	11.0
	15	7	7.0	5.6	32.9	5	4.9	3.4	13.8	7	8.7	4.4	21.5	7	14.8	4.5	21.2	7	5.8	3.7	9.5
	19	7	6.6	4.2	11.2	5	5.7	3.3	12.5	7	4.6	1.7	14.4	7	9.6	3.5	16.6	7	5.1	3.0	11.6
Cortisol	-0	7	336	211	358	5	372	306	407	7	320	194	420	7	336	208	455	7	254	152	493
(0.69)	1	7	289	170	363	5	258	197	316	7	245	154	483	7	346	162	486	7	278	179	347
	6	7	275	202	425	5	267	220	372	7	247	165	505	7	306	168	403	7	275	147	378
	13	7	274	183	425	5	246	226	417	7	246	179	400	7	358	171	418	7	252	149	296
	14	7	371	248	598	5	263	214	464	7	296	172	405	7	335	277	407	7	261	125	363
	15	7	257	237	502	5	286	222	422	7	324	232	530	7	364	267	433	7	285	237	362
	19	7	266	219	343	5	314	200	373	7	266	175	460	7	309	148	422	7	241	180	368
Cortisone	-0	7	58.4	53.5	62.4	5	52.0	49.6	61.4	7	62.7	54.6	76.3	7	50.0	47.3	69.5	7	56.8	44.3	67.3
(0.069)	1	7	53.9	50.2	70.8	5	47.5	42.5	62.8	7	57.4	47.1	71.3	7	48.8	38.5	74.4	7	55.3	48.1	65.6
	6	7	58.8	54.2	63.7	5	47.7	41.4	65.4	7	55.7	51.5	70.5	7	45.3	34.7	64.9	7	47.3	37.9	68.4
	13	7	52.6	50.4	65.6	5	47.2	40.0	65.1	7	58.0	47.8	66.9	7	49.2	36.9	66.5	7	46.5	38.7	53.9
	14	7	59.9	56.0	70.9	5	49.4	40.6	63.9	7	62.9	52.4	66.3	7	51.2	42.2	67.3	7	45.3	29.7	54.6
	15	7	59.6	53.7	75.2	5	48.6	43.2	70.8	7	65.2	50.4	69.8	7	51.7	44.7	70.9	7	51.9	40.3	63.3
	19	7	54.6	48.4	76.4	5	43.6	37.1	66.9	7	62.1	51.0	64.7	7	46.4	42.9	66.9	7	50.9	39.8	71.4

		Placebo				3 mg QD				30 mg QD				60 mg BID				90 mg QD		
Analyte (LLOQ)	**Day**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
Dehydroepiandrosterone	-0	7	4.6	3.0	11.3	5	6.9	5.3	12.4	7	6.4	4.3	12.8	7	5.9	3.0	7.1	7	6.3	2.5	9.1
(0.416)	1	7	4.3	3.2	10.2	5	4.9	3.4	9.4	7	8.5	3.4	12.2	7	5.0	4.2	7.6	7	4.8	3.3	8.6
	6	7	4.3	3.7	13.3	5	6.3	4.5	9.3	7	7.4	2.1	13.3	7	4.8	2.7	7.5	7	5.0	2.9	12.3
	13	7	3.8	3.0	8.0	5	5.3	3.7	12.0	7	5.1	2.8	11.0	7	4.9	2.4	6.7	7	4.3	1.7	6.2
	14	7	7.4	3.6	12.6	5	5.9	3.7	10.9	7	5.9	3.0	112.0	7	5.6	3.1	9.1	7	3.6	2.9	5.6
	15	7	4.1	3.1	8.6	5	4.7	3.9	11.8	7	7.5	2.4	24.7	7	5.6	3.3	8.9	7	4.3	2.3	7.7
	19	7	3.5	3.4	8.8	5	4.1	3.2	10.7	7	6.9	3.0	10.9	7	5.0	4.1	8.9	7	5.7	2.5	8.2
Dehydroepiandrosterone sulfate	-0	7	1557	864	2756	5	1954	1522	3546	7	2199	588	3669	7	1463	806	2555	7	2150	612	4725
	1	7	1299	754	2228	5	1873	1278	3075	7	2624	755	3947	7	1465	993	3249	7	2289	800	5494
(49.9)	6	7	1664	979	3317	5	2049	1578	3726	7	3655	881	4554	7	2154	1401	4376	7	2649	909	6522
	13	7	1526	763	2815	5	1858	1369	4053	7	2336	791	3978	7	1461	1153	3325	7	2282	673	5692
	14	7	1248	855	2489	5	2100	1488	3845	7	2492	875	3439	7	1828	884	2897	7	2202	693	5112
	15	7	1280	1041	2929	5	2630	1595	4270	7	2742	685	4706	7	1405	1137	3099	7	2057	744	5271
	19	7	1478	882	2749	5	1890	1411	4369	7	2363	765	3012	7	1499	1096	2883	7	1921	683	4867
Dihydrotestosterone	-0	5	0.12	0.00	0.23	5	0.22	0.13	0.56	7	0.11	0.00	0.59	4	0.14	0.12	0.16	6	0.16	0.12	0.32
(0.041)	1	5	0.14	0.12	0.26	5	0.30	0.17	0.58	7	0.09	0.06	0.61	3	0.22	0.13	0.36	6	0.26	0.14	0.46
	6	6	0.17	0.15	0.29	4	0.33	0.17	0.48	7	0.20	0.04	0.71	7	0.20	0.14	0.25	7	0.31	0.16	0.58
	13	5	0.20	0.12	0.23	4	0.32	0.17	0.48	7	0.12	0.04	0.60	7	0.27	0.19	0.34	7	0.29	0.18	0.48
	14	5	0.17	0.06	0.22	5	0.35	0.14	0.57	7	0.18	0.03	0.67	6	0.29	0.19	0.47	7	0.33	0.22	0.57
	15	5	0.19	0.00	0.24	5	0.32	0.14	0.55	7	0.16	0.07	0.65	5	0.23	0.16	0.37	6	0.28	0.25	0.42
	19	4	0.20	0.04	0.22	5	0.23	0.14	0.56	7	0.08	0.00	0.49	5	0.15	0.12	0.21	5	0.20	0.16	0.31
17ß-estradiol	-0	3	0.024	0.004	0.027	4	0.025	0.014	0.197	7	0.008	0.001	0.019	3	0.017	0.017	0.032	3	0.013	0.013	0.022
(0.018)	1	4	0.013	0.004	0.041	3	0.063	0.021	0.118	7	0.011	0.003	0.097	2	0.020	0.019	0.021	2	0.017	0.017	0.017
	6	5	0.016	0.000	0.029	4	0.026	0.012	0.177	7	0.015	0.007	0.023	1	0.015	0.015	0.015	1	0.017	0.017	0.017
	13	3	0.008	0.005	0.021	4	0.026	0.020	0.474	7	0.007	0.000	0.028	2	0.037	0.023	0.051	2	0.021	0.018	0.025
	14	4	0.010	0.000	0.020	4	0.022	0.015	0.121	7	0.007	0.000	0.024	2	0.023	0.022	0.024	5	0.013	0.013	0.025
	15	3	0.014	0.006	0.021	4	0.021	0.014	0.516	7	0.008	0.000	0.033	0	-	-	-	1	0.020	0.020	0.020
	19	4	0.015	0.007	0.028	3	0.021	0.013	0.167	7	0.008	0.000	0.028	2	0.026	0.016	0.035	1	0.016	0.016	0.016
Estrone	-0	3	0.083	0.049	0.087	4	0.081	0.063	0.373	7	0.052	0.039	0.105	3	0.084	0.053	0.126	6	0.058	0.041	0.094
(0.111)	1	4	0.060	0.038	0.096	4	0.094	0.043	0.105	7	0.066	0.046	0.136	4	0.072	0.048	0.113	6	0.065	0.043	0.104
	6	4	0.056	0.041	0.071	4	0.077	0.046	0.154	7	0.066	0.026	0.118	3	0.087	0.039	0.094	7	0.061	0.041	0.085
	13	4	0.054	0.048	0.078	4	0.086	0.058	0.517	7	0.061	0.040	0.113	3	0.059	0.049	0.080	3	0.049	0.040	0.056
	14	6	0.042	0.037	0.107	4	0.076	0.050	0.181	7	0.058	0.000	0.088	3	0.106	0.038	0.120	3	0.053	0.042	0.067
	15	4	0.054	0.051	0.076	3	0.111	0.073	0.422	7	0.044	0.000	0.135	2	0.104	0.096	0.112	4	0.044	0.040	0.052
	19	4	0.077	0.041	0.095	5	0.065	0.040	0.215	7	0.044	0.037	0.076	3	0.087	0.055	0.145	6	0.053	0.039	0.066

		Placebo				3 mg QD				30 mg QD				60 mg BID				90 mg QD		
Analyte (LLOQ)	**Day**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
Etiocholanolone	-0	4	0.12	0.04	0.18	4	0.19	0.09	0.21	7	0.16	0.09	0.28	4	0.21	0.14	0.29	5	0.18	0.07	0.25
(0.207)	1	4	0.15	0.10	0.25	4	0.20	0.10	0.28	7	0.18	0.06	0.29	5	0.28	0.08	0.38	5	0.24	0.12	0.34
	6	4	0.13	0.10	0.19	4	0.19	0.10	0.25	7	0.31	0.08	0.37	7	0.24	0.12	0.67	6	0.44	0.16	0.58
	13	5	0.14	0.07	0.18	4	0.19	0.08	0.26	7	0.18	0.14	0.33	7	0.26	0.13	0.56	6	0.33	0.19	0.51
	14	6	0.14	0.07	0.28	4	0.19	0.08	0.27	7	0.26	0.16	0.30	7	0.35	0.09	0.50	7	0.28	0.08	0.51
	15	5	0.13	0.07	0.24	3	0.19	0.15	0.27	7	0.24	0.12	0.34	7	0.24	0.08	0.46	6	0.36	0.14	0.59
	19	5	0.11	0.09	0.18	4	0.17	0.07	0.22	7	0.17	0.11	0.25	5	0.24	0.08	0.39	6	0.24	0.08	0.47
Progesterone	-0	7	0.12	0.07	0.17	5	0.13	0.07	0.17	7	0.11	0.07	0.11	7	0.09	0.07	0.19	7	0.11	0.07	0.15
(0.048)	1	7	0.12	0.08	0.17	5	0.12	0.08	0.20	7	0.10	0.08	0.25	7	0.10	0.07	0.26	7	0.12	0.06	0.14
	6	7	0.13	0.07	0.28	5	0.10	0.08	0.14	7	0.10	0.07	0.18	7	0.11	0.07	0.14	7	0.11	0.07	0.14
	13	7	0.11	0.07	0.13	5	0.09	0.07	0.15	7	0.09	0.06	0.14	7	0.10	0.06	0.16	7	0.08	0.06	0.13
	14	7	0.12	0.10	0.22	5	0.11	0.08	0.16	7	0.09	0.06	0.16	7	0.11	0.08	0.17	7	0.10	0.07	0.17
	15	7	0.10	0.09	0.16	5	0.09	0.08	0.15	7	0.11	0.08	0.22	7	0.09	0.07	0.18	7	0.09	0.07	0.14
	19	7	0.11	0.08	0.14	5	0.09	0.08	0.13	7	0.09	0.06	0.20	7	0.10	0.07	0.13	7	0.08	0.06	0.16
Testosterone	-0	7	0.44	0.25	0.52	5	0.39	0.34	0.73	7	0.47	0.31	0.59	7	0.51	0.38	0.71	7	0.41	0.30	1.07
(0.01)	1	7	0.47	0.22	0.59	5	0.41	0.31	0.71	7	0.47	0.28	0.64	7	0.47	0.40	0.67	7	0.36	0.26	0.89
	6	7	0.44	0.23	0.51	5	0.38	0.31	0.70	7	0.37	0.25	0.55	7	0.42	0.32	0.51	7	0.30	0.23	0.79
	13	7	0.39	0.28	0.50	5	0.31	0.29	0.72	7	0.39	0.26	0.60	7	0.39	0.30	0.60	7	0.28	0.24	0.73
	14	7	0.54	0.29	0.62	5	0.40	0.30	0.74	7	0.43	0.12	0.49	7	0.47	0.34	0.76	7	0.30	0.26	0.81
	15	7	0.47	0.19	0.57	5	0.34	0.28	0.84	7	0.48	0.30	0.62	7	0.51	0.39	0.81	7	0.31	0.25	0.91
	19	7	0.42	0.24	0.58	5	0.31	0.25	0.69	7	0.47	0.37	0.65	7	0.52	0.48	0.79	7	0.39	0.32	1.03

BID, twice daily; LLOQ, lower limit of quantitation; Max, maximum; Min, minimum; N, number of valid cases; QD, once daily.
Invalid values and values below the limit of detection were excluded from statistics.

Suppl. Table 3: PK parameters of BAY1128688 and its metabolite M-7 in plasma (geometric mean/%CV) obtained after single and multiple oral administration of different doses of BAY1128688 to *post*- and *pre*menopausal women

Analyte	Parameter	Unit	Dose group			
			***(A) Post*menopausal women**			
			3 mg QD (N=5)	**30 mg QD (N=7)**	**90 mg QD (N=7)**	**60 mg BID (N=7)**
			Single-dose administration (Day 1/Period 1)			
Parent drug	C_{max}	µg/L	141 / 21.5	2060 / 23.6	6960 / 19.6	3650 / 52.9
	C_{max}/D	1/L	0.0469 / 21.5	0.0687 / 23.6	0.0773 / 19.6	0.0608 / 52.9
	t_{max}	h	3.00 (1.48–3.97) [a]	2.02 (0.983–3.05) [a]	1.52 (0.983-3.05) [a]	2.02 (1.02-5.98) [a]
	AUC(0-24)	µg·h/L	1420 / 32.2	15600 / 22.7	56200 / 18.0	23400 / 34.6 [b]
	AUC	µg·h/L	2430 / 50.8 [c]	20400 / 27.8	71300 / 23.3	42400 / 33.5
	AUC/D	h/L	0.810 / 50.8 [c]	0.680 / 27.8	0.792 / 23.3	0.706 / 33.5
	$t_{1/2}$	h	25.1 / 15.8 [c]	27.5 / 44.9	31.0 / 29.5	23.1 / 21.9
M-7	AUC	µg/L	n.c.	2060 / 36.4 [d]	4500 / 30.4 [d]	6830 / 45.3 [e]
	MR	---	0.0149 / 117	0.0234 / 25.5	0.0080 / 30.5	0.0231 / 23.7
			Multiple-dose administration (Day 14/Period 2)			
Parent drug	$C_{max,MD}$	µg/L	207 / 36.8	1990 / 18.7	8510 / 21.7	7220 / 43.1
	C_{max}/D_{MD}	1/L	0.0689 / 36.8	0.0662 / 18.7	0.0946 / 21.7	0.0601 / 43.1
	$t_{max,MD}$	h	1.50 (0.967-3.95) [a]	2.97 (1.48-6.00) [a]	3.00 (1.50-3.02) [a]	2.03 (0.983-3.07) [a]
	$C_{min,MD}$	µg/L	48.8 / 76.9	265 / 28.0	1150 / 43.5	2640 / 47.7
	$AUC(0\text{-}24)_{MD}$	µg·h/L	2280 / 52.7	19200 / 17.3	79100 / 26.0	109000 / 41.8 [g]
	$AUC(0\text{-}24)/D_{MD}$	h/L	0.762 / 52.7	0.640 / 17.3	0.879 / 26.0	0.905 / 41.8 [f, g]
	R_AAUC	---	1.61 / 25.6	1.23 / 9.06	1.41 / 12.9	2.32 / 25.3
	R_{LIN}		1.02 / 17.6 [c]	0.940 / 13.2	1.11 / 12.9	1.28 / 19.2
M-7	$AUC(0\text{-}24)_{MD}$	µg·h/L	225 / 64.1	2060 / 31.3	8800 / 40.6	10200 / 38.2 [g]
	R_AAUC	---	[16.1 / 157] [c]	6.90 / 21.0	8.31 / 31.9	{33.3 / 50.0}
	MR	---	0.121 / 65.5	0.132 / 16.0	0.136 / 26.0	0.115 / 34.0

Continued next page

(B) ***Pre*menopausal women**

			60 mg QD (N=9)	60 mg BID (N=9)
			Multiple-dose administration (Day >14 [h]/Treatment Cycle)	
	$C_{max,MD}$	µg/L	4340 / 24.8	6800 / 23.3
	C_{max}/D_{MD}	1/L	0.0724 / 24.8	0.0567 / 23.3
	$t_{max,MD}$	h	2.0 (1.5 - 4.0) [a]	1.93 (1.0 - 4.0) [a]
	$C_{min,MD}$	µg/L	641 / 57.9	2260 / 40.4
	$AUC(0\text{-}24)_{MD}$	µg·h/L	42800 / 29.8	98000 / 25.0 [g]
	$AUC(0\text{-}24)/D_{MD}$	h/L	0.713 / 29.8	0.817 / 25.0 [f, g]
M-7	$AUC(0\text{-}24)_{MD}$	µg·h/L	3070 / 79.2	7160 / 60.3 [g]
	MR	---	0.0878 / 55.8	0.0895 / 41.4

AUC, area under the plasma concentration vs time curve from zero to infinity after single (first) dose; AUC(0-t), AUC from time zero to time t hours post dose; BID, twice per day; C_{max}, maximum observed concentration in plasma (within the dosing interval); C_{min}, observed plasma concentration within the dosing interval; D, dose; MD, multiple dose; MR, metabolite AUC(0-24) to parent drug AUC(0-24) ratio (molecular weight adjusted); n.c., not calculated; QD, once per day; R_AAUC, accumulation ratio = $AUC(0\text{-}24)_{multiple\ dose}/AUC(0\text{-}24)_{single\ dose}$; R_{LIN}, linearity index = $AUC(0\text{-}24)_{multiple\ dose}/AUC$; $t_{1/2}$, half-life associated with the terminal slope; t_{max}, time to reach maximum drug concentration in plasma. (The time courses of trough concentrations indicate that PK steady state had been reached when the samples for multiple-dose PK profiles were taken (i.e., DAY14/Period 2 in postmenopausal women and Day≥15/Treatment Cycle in premenopausal women.)

[ ] implausible due to low concentrations of BAY1107202 after single dosing in period 1 and applied detection limit; { } implausible due to low AUC(0-12) of BAY1107202 after single dosing in period 1.

[a] median (range); [b] AUC(0-12); [c] n=4; [d] N=5; [e] n=6; [f] D = 2 · 60 mg = 120 mg; [g] extrapolated from AUC(0-12); [h] any day between Day 15 and Day 28.

Suppl. Table 4: Most common treatment-emergent adverse events (*post*- and *pre*menopausal women) – incidences without consideration of the drug-event relationship and incidences for events which the investigator considered study-drug related

MedDRA preferred term	**Postmenopausal women, Placebo, Part A** (N=7)		**Postmenopausal women BAY1128688, Part A** (N=26)		**Premenopausal women BAY1128688, Part B** (N=18)	
	All	***Drug-related***	**All**	***Drug-related***	**All**	***Drug-related***
Headache	0 (0%)	*0*	7 (26.9%)	*6 (23.1%)*	7 (38.9%)	*5 (27.8%)*
Nausea	3 (42.9%)	*3 (42.9%)*	4 (15.4%)	*4 (15.4%)*	4 (22.2%)	*4 (22.2%)*
Serum bilirubin increased	0 (0%)	*0*	7 (26.9%)	*7 (26.9%*	1 (5.6%)	*1 (5.6%)*
Vomiting	2 (28.6%)	*2 (28.6%)*	4 (15.4%)	*3 (11.5%)*	2 (11.1%)	*2 (11.1%)*
Nasopharyngitis	1 (14.3%)	*0*	2 (7.7%)	*0*	4 (22.2%)	*0*
Decreased appetite	0	*0*	4 (15.4%)	*4 (15.4%)*	1 (5.6%)	*1 (5.6%)*

Numbers indicate the number of participants affected. Percentages refer to the total number of participants who received the respective treatment.

Suppl. Table 5: Treatment-emergent adverse events (*post*- and *pre*menopausal women)

	Postmenopausal women										Premenopausal women	
Primary System Organ Class Preferred Term MedDRA version 18.1	**Placebo Single dose N=7 (100%)**	**Placebo 14 d N=7 (100%)**	**3 mg Single dose N=5 (100%)**	**3 mg 14 d N=5 (100%)**	**30 mg Single dose N=7 (100%)**	**30 mg 14 d N=7 (100%)**	**60 mg Single dose N=7 (100%)**	**60 mg BID 14 d N=7 (100%)**	**90 mg Single dose N=7 (100%)**	**90 mg 14 d N=7 (100%)**	**60 mg 28 d N=9 (100%)**	**60 mg BID 28 d N=9 (100%)**
Number of subjects (%) with at least one such adverse event	*3 (42.9%)*	*6 (85.7%)*	*4 (80.0%)*	*3 (60.0%)*	*3 (42.9%)*	*5 (71.4%)*	*3 (42.9%)*	*6 (85.7%)*	*2 (28.6%)*	*6 (85.7%)*	*5 (55.6%)*	*6 (66.7%)*
Gastrointestinal disorders	**1 (14.3%)**	**2 (28.6%)**	**2 (40.0%)**	**0**	**1 (14.3%)**	**3 (42.9%)**	**0**	**0**	**1 (14.3%)**	**1 (14.3%)**	**2 (22.2%)**	**3 (33.3%)**
Abdominal distension	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Abdominal pain lower	0	0	2 (40.0%)	0	0	0	0	0	0	0	0	0
Constipation	0	1 (14.3%)	0	0	0	0	0	0	0	0	0	0
Nausea	1 (14.3%)	2 (28.6%)	0	0	1 (14.3%)	3 (42.9%)	0	0	0	1 (14.3%)	2 (22.2%)	2 (22.2%)
Vomiting	1 (14.3%)	1 (14.3%)	0	0	0	2 (28.6%)	0	0	1 (14.3%)	1 (14.3%)	1 (11.1%)	1 (11.1%)
Paraesthesia oral	0	0	0	0	0	0	0	0	0	0	0	1 (11.1%)
General disorders and administration site conditions	**0**	**2 (28.6%)**	**0**	**0**	**1 (14.3%)**	**2 (28.6%)**	**1 (14.3%)**	**3 (42.9%)**	**0**	**1 (14.3%)**	**1 (11.1%)**	**0**
Application site erythema	0	0	0	0	1 (14.3%)	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	1 (14.3%)	0	0	1 (11.1%)	0
Application site inflammation	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Vessel puncture site haematoma	0	0	0	0	0	1 (14.3%)	0	0	0	0	0	0
Vessel puncture site pain	0	0	0	0	0	0	1 (14.3%)	0	0	0	0	0
Medical device site erythema	0	1 (14.3%)	0	0	0	1 (14.3%)	1 (14.3%)	2 (28.6%)	0	0	0	0
Medical device site haematoma	0	0	0	0	0	0	0	1 (14.3%)	0	0	0	0
Medical device site pruritus	0	1 (14.3%)	0	0	0	0	0	1 (14.3%)	0	0	0	0
Immune system disorders	**0**	**1 (14.3%)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Allergy to arthropod sting	0	1 (14.3%)	0	0	0	0	0	0	0	0	0	0
Infections and infestations	**1 (14.3%)**	**0**	**0**	**1 (20.0%)**	**0**	**0**	**0**	**1 (14.3%)**	**0**	**2 (28.6%)**	**2 (22.2%)**	**3 (33.3%)**
Nasopharyngitis	1 (14.3%)	0	0	1 (20.0%)	0	0	0	1 (14.3%)	0	0	1 (11.1%)	3 (33.3%)
Tonsillitis	0	0	0	0	0	0	0	0	0	0	1 (11.1%)	0
Urinary tract infection	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Oral herpes	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**0**	**0**	**1 (14.3%)**	**0**	**0**	**1 (14.3%)**	**0**	**0**
Arthropod sting	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0

	Postmenopausal women										Premenopausal women	
Primary System Organ Class Preferred Term MedDRA version 18.1	**Placebo Single dose N=7 (100%)**	**Placebo 14 d N=7 (100%)**	**3 mg Single dose N=5 (100%)**	**3 mg 14 d N=5 (100%)**	**30 mg Single dose N=7 (100%)**	**30 mg 14 d N=7 (100%)**	**60 mg Single dose N=7 (100%)**	**60 mg BID 14 d N=7 (100%)**	**90 mg Single dose N=7 (100%)**	**90 mg 14 d N=7 (100%)**	**60 mg 28 d N=9 (100%)**	**60 mg BID 28 d N=9 (100%)**
Fall	0	0	0	0	0	0	1 (14.3%)	0	0	0	0	0
Subcutaneous haematoma	0	0	0	0	0	0	1 (14.3%)	0	0	0	0	0
Investigations	**0**	**3 (42.9%)**	**1 (20.0%)**	**0**	**1 (14.3%)**	**2 (28.6%)**	**0**	**5 (71.4%)**	**2 (28.6%)**	**4 (57.1%)**	**1 (11.1%)**	**0**
Aspartate aminotransferase increased	0	0	0	0	0	1 (14.3%)	0	0	0	0	0	0
Blood bilirubin increased	0	0	1 (20.0%)	0	0	0	0	5 (71.4%)	1 (14.3%)	1 (14.3%)	1 (11.1%)	0
Blood cholesterol increased	0	1 (14.3%)	0	0	1 (14.3%)	0	0	0	0	0	0	0
Blood fibrinogen decreased	0	1 (14.3%)	0	0	0	0	0	0	0	0	0	0
Blood fibrinogen increased	0	0	0	0	0	0	0	0	1 (14.3%)	2 (28.6%)	0	0
Eosinophil count increased	0	0	0	0	0	0	0	1 (14.3%)	0	0	0	0
Blood urine present	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0	0	1 (14.3%)	0	0
Low density lipoprotein increased	0	2 (28.6%)	0	0	0	0	0	0	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Protein total decreased	0	0	0	0	0	0	0	0	0	1 (14.3%)	0	0
Red blood cells urine positive	0	0	0	0	0	1 (14.3%)	0	0	0	1 (14.3%)	0	0
Nitrite urine present	0	0	0	0	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**0**	**1 (14.3%)**	**0**	**0**	**0**	**3 (42.9%)**	**0**	**1 (11.1%)**
Decreased appetite	0	0	0	0	0	1 (14.3%)	0	0	0	3 (42.9%)	0	1 (11.1%)
Musculoskeletal and connective tissue disorders	**1 (14.3%)**	**1 (14.3%)**	**2 (40.0%)**	**0**	**0**	**1 (14.3%)**	**1 (14.3%)**	**0**	**0**	**0**	**0**	**0**
Back pain	1 (14.3%)	1 (14.3%)	0	0	0	0	0	0	0	0	0	0
Myalgia	0	0	1 (20.0%)	0	0	0	0	0	0	0	0	0
Pain in extremity	0	0	1 (20.0%)	0	0	0	0	0	0	0	0	0
Muscle tightness	0	0	0	0	0	0	1 (14.3%)	0	0	0	0	0
Spinal pain	0	0	0	0	0	1 (14.3%)	0	0	0	0	0	0
Nervous system disorders	**0**	**1 (14.3%)**	**1 (20.0%)**	**3 (60.0%)**	**1 (14.3%)**	**2 (28.6%)**	**0**	**1 (14.3%)**	**0**	**1 (14.3%)**	**3 (33.3%)**	**4 (44.4%)**
Dizziness	0	1 (14.3%)	0	0	0	0	0	0	0	0	0	0
Headache	0	0	0	3 (60.0%)	1 (14.3%)	1 (14.3%)	0	1 (14.3%)	0	1 (14.3%)	3 (33.3%)	4 (44.4%)
Paraesthesia	0	0	1 (20.0%)	1 (20.0%)	0	0	0	0	0	0	0	0
Somnolence	0	0	0	0	0	1 (14.3%)	0	0	0	0	0	0
Renal and urinary disorders	**0**	**0**	**0**	**0**	**0**	**1 (14.3%)**	**0**	**0**	**0**	**2 (28.6%)**	**0**	**0**
Renal pain	0	0	0	0	0	1 (14.3%)	0	0	0	2 (28.6%)	0	0

	----------				Postmenopausal women					----------	Premenopausal women	
Primary System Organ Class **Preferred Term** **MedDRA version 18.1**	**Placebo Single dose N=7 (100%)**	**Placebo 14 d N=7 (100%)**	**3 mg Single dose N=5 (100%)**	**3 mg 14 d N=5 (100%)**	**30 mg Single dose N=7 (100%)**	**30 mg 14 d N=7 (100%)**	**60 mg Single dose N=7 (100%)**	**60 mg BID 14 d N=7 (100%)**	**90 mg Single dose N=7 (100%)**	**90 mg 14 d N=7 (100%)**	**60 mg 28 d N=9 (100%)**	**60 mg BID 28 d N=9 (100%)**
Respiratory, thoracic and mediastinal disorders	**1 (14.3%)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Cough	1 (14.3%)	0	0	0	0	0	0	0	0	0	0	0

BID, twice daily. The drug was given once (daily), unless indicated otherwise.

Numbers indicate the number of participants affected. Percentages refer to the total number of participants who received the respective treatment.

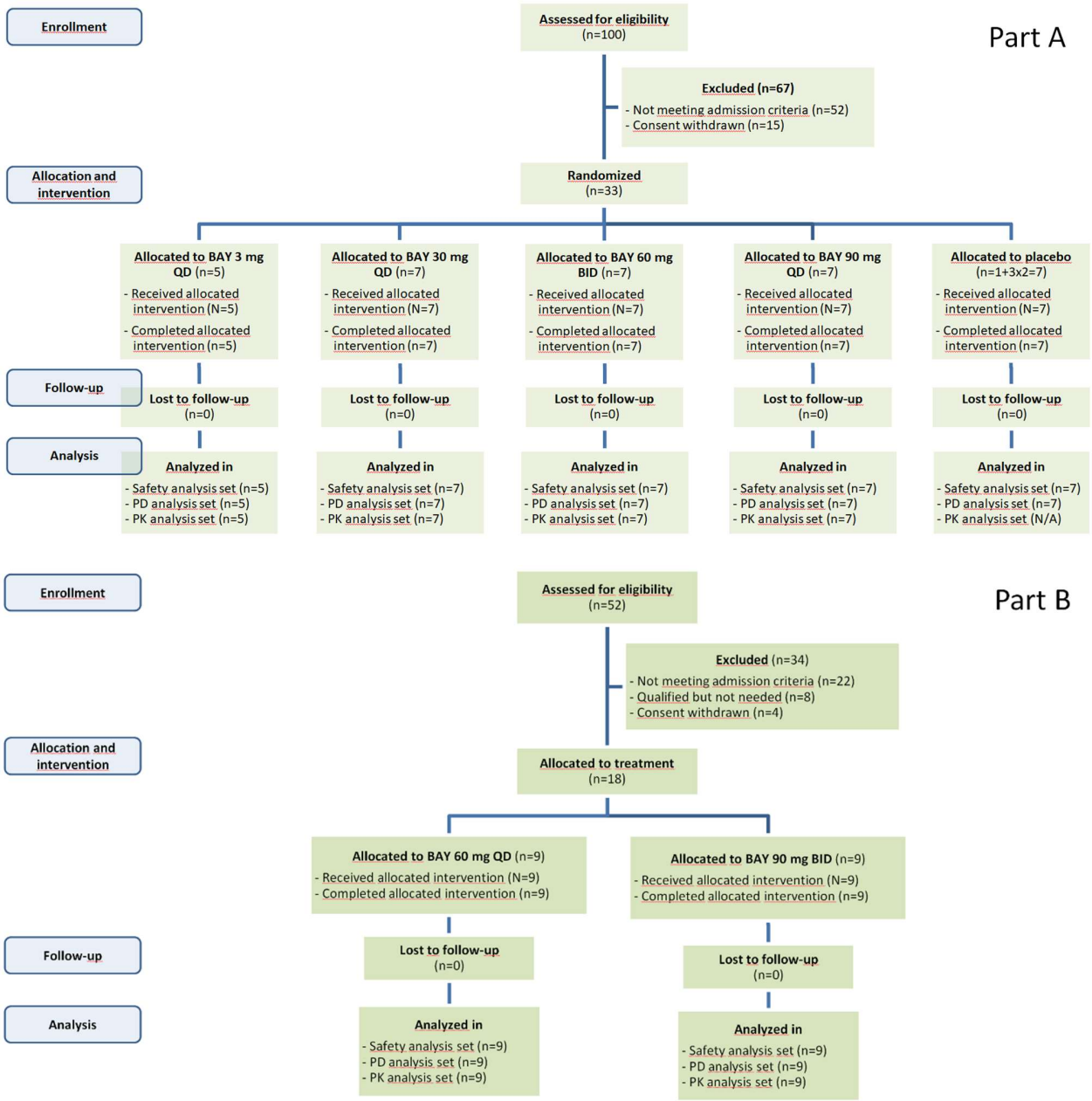
Suppl. Table 6: Androsterone, etiocholanolone, and DHT in serum: Minimum and maximum concentrations observed and reference ranges for healthy premenopausal women

	N	Androsterone [nM] [a]	Etiocholanolone [nM] [a]	Dihydrotestosterone (DHT) [nM] [a]
Pre-treatment cycle [a]	18	0.138 – 1.824	<0.069 [b] – 1.119	0.193 – 0.928
Treatment period [a]	18	0.225 – 6.360	<0.069 [b] – 1.750	0.240 – 1.190
Shiraishi et al. (1)	133	n.a.	n.a.	0.09 – 0.91
Rothman et al. (2)	29	n.a.	n.a.	(0.316 ± 0.023) [d, e]
Mezzulo et al. (3)	118	n.a.	n.a.	<0.134 – 0.675
Ke et al., 2017 (4)	10	0.164 – 1.066	n.a.	n.a.

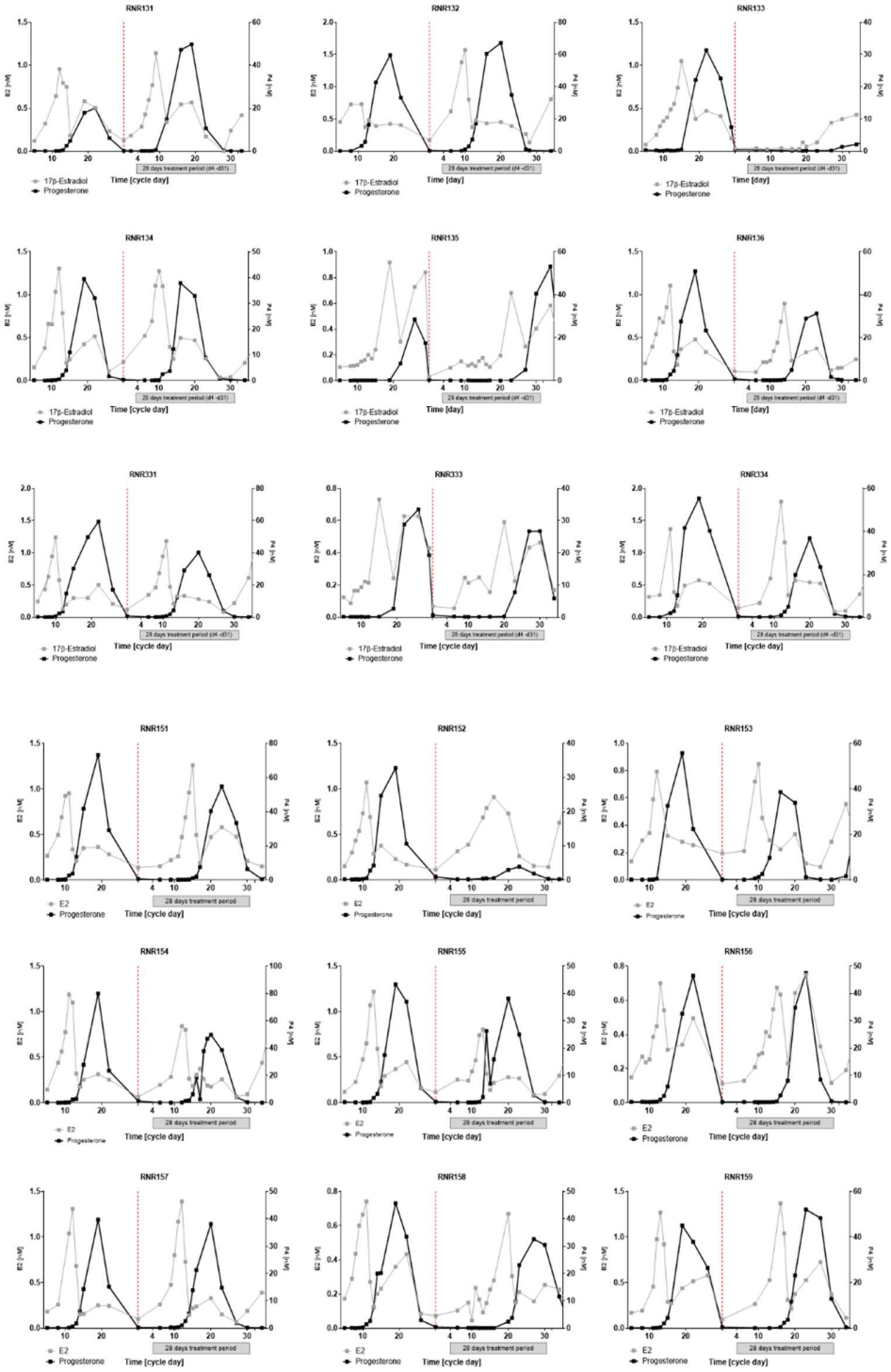
[a] Note: Multiple measurements were conducted for each subject throughout the menstrual cycle. Values were converted to meet nM by multiplication factor of 0.0344 from ng/dL. The molecular weight is quite similar for all three steroids (androsterone: 290.447 g/mol; etiocholanolone: 290.445 g/mol; DHT: 290.442 g/mol); [b] ranges were calculated based on all available data, i.e., 8 to 11 data points per participant in the pre- treatment period and 7 to 12 data points per participant in the treatment period; [c] limit of detection; [d] samples were taken during the early follicular phase; [e] mean ± standard deviation. n.a., not applicable.

2.2 Supplemental figures

Suppl. Figure 1: Subject disposition

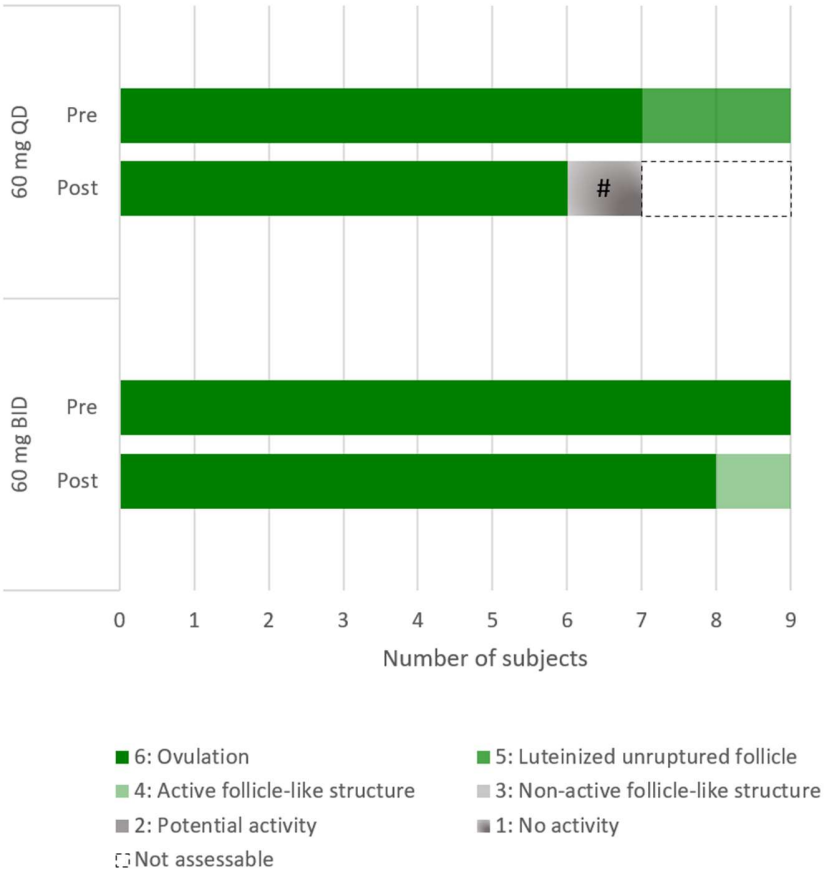


Suppl. Figure 2: Individual estradiol and progesterone serum concentrations before and during treatment with BAY1128688 60 mg QD and BID (premenopausal women)



Pronounced/sharp/distinct# estradiol and progesterone peaks can be considered as indicative of intact ovulatory cycles.

Suppl. Figure 3: Ovarian activity (Hoogland scores) before and during treatment with BAY1128688 60 mg QD and BID (*pre*menopausal women)



The Hoogland score is a combination score based on (1) the diameter of the largest follicle-like structure (FLS) in either ovary, (2) the concentration of estradiol (E2) in serum, and (3) the concentration of progesterone (P) in serum (Hoogland HJ & Skouby SO. Contraception 1993; 47(6):583–90).

	Scoring criteria			
Score		**FLS diameter** [mm]	**E2** [nmol/L]	**P** [nmol/L]
1	No activity	≤ 10	--	--
2	Potential activity	> 10	--	--
3	Non-active follicle-like structure	> 13	≤ 0.1	--
4	Active follicle-like structure	> 13	> 0.1	≤ 5
5	Luteinized unruptured follicle	> 13, persisting	> 0.1	> 5
6	Ovulation	> 13, ruptured	> 0.1	> 5

#, Elevated serum follicle-stimulating hormone values during treatment (maximum (cycle day 17): 36.0 U/L, ULN 19 U/L), which decreased again after treatment, intra-cyclic bleeding were interpreted as signs of a perimenopausal state of the participant.

2.3 Population pharmacokinetic modeling

The developed popPK model consisted structurally of a depot, central and peripheral compartments for both tablet formulation and solution as well as four additional transit compartments for the tablet formulation. Absorption was modeled by a first order process for both formulations, including a lag time in absorption for the tablet formulation. The elimination of the drug from the central compartment followed Michaelis-Menten kinetics. Random effect parameters accounting for inter-individual variability (IIV) were associated to the maximum elimination rate from the central compartment (V_{max}), the apparent volume of the central compartment (V_C/F), and the absorption rate constants (k_1 for the solution and k_2 for the tablet formulation, same IIV). To account for any unexplained variability, two residual error terms were included for the solution and tablet formulation separately. For the parameter V_C/F body weight (increased V_C/F) and the administered BAY1128688 dose (for ≤10 mg: V_C/F decreased with dose) were identified as covariates. Furthermore, the parameter V_{max} increased with the administered BAY1128688 dose up to 10 mg. To account for food effects, a two-population mixture model was introduced for the absorption rate constant of the tablet formulation under fed conditions. Moreover, a fixed bioavailability parameter was used when estimating plasma concentrations of BAY1128688 under fed condition.

A visual predictive check (1000 simulations of the study described in this paper) confirmed that the selected popPK model was able to adequately account for the observed plasma exposure of BAY1128688 in both study parts. Hence, it was concluded that both premenopausal and postmenopausal women exhibited the same plasma exposure of BAY1128688.

The developed popPK model for BAY1128688 set the base for further popPK/PD modelling, e.g., describing the BAY1128688 concentration dependent effect on serum bilirubin over time (see main manuscript text, section 3.4).

2.4 Evaluation of renal safety

No early signs of kidney damage were detected as the mean values of kidney safety markers KIM-1, neutrophil gelatinase-associated lipocalin, albumin, cystatin C, and creatinine were not changed in a relevant way at the end of the multiple-dose treatment compared to pre-treatment values and values during placebo treatment (data on file; Bayer AG).

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