Supplemental Material to:

Paroxetine markedly increases plasma concentrations of ophthalmic timolol; CYP2D6 inhibitors may increase the risk of cardiovascular adverse effects of 0.5% timolol eye drops

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Drug Metabolism & Disposition

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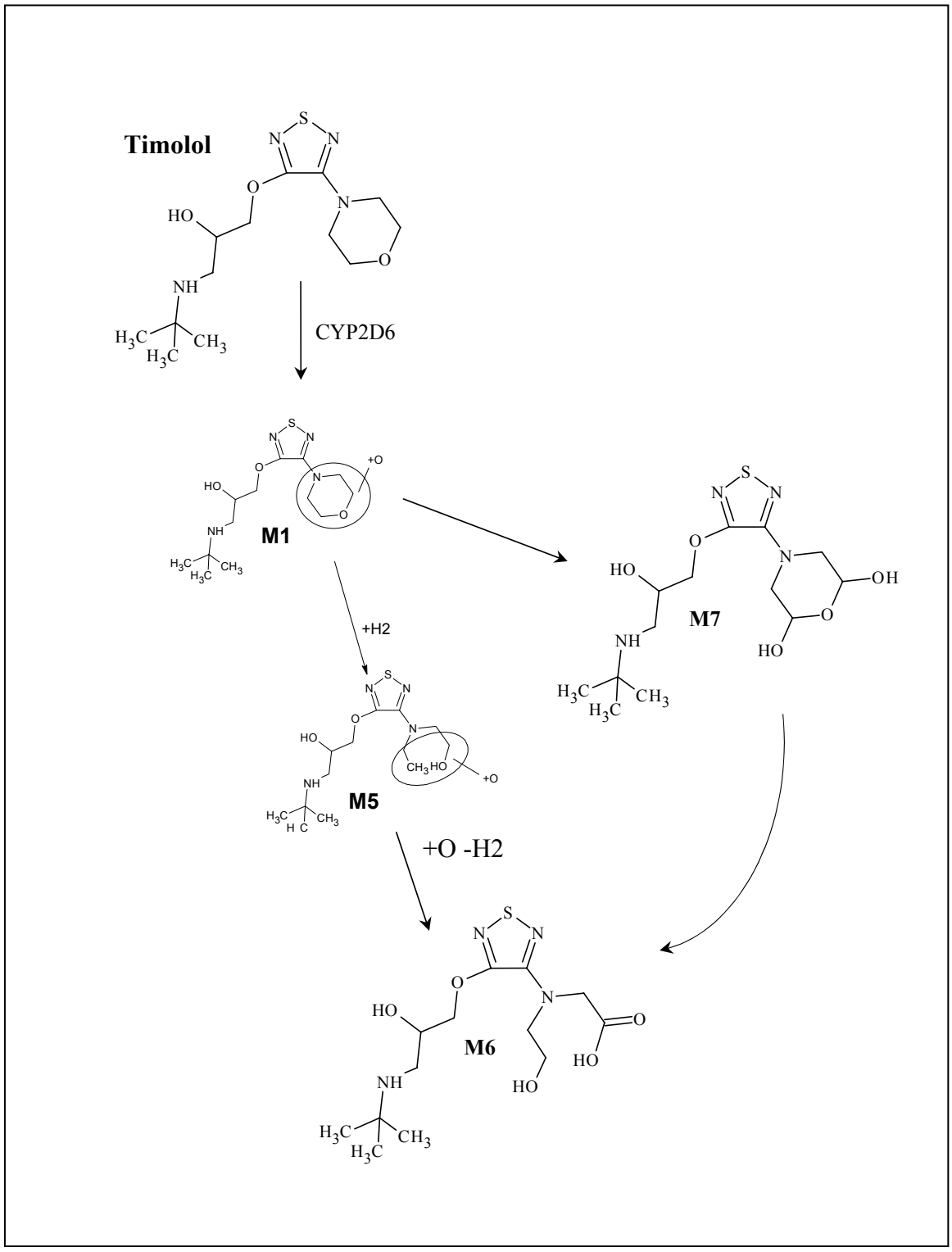
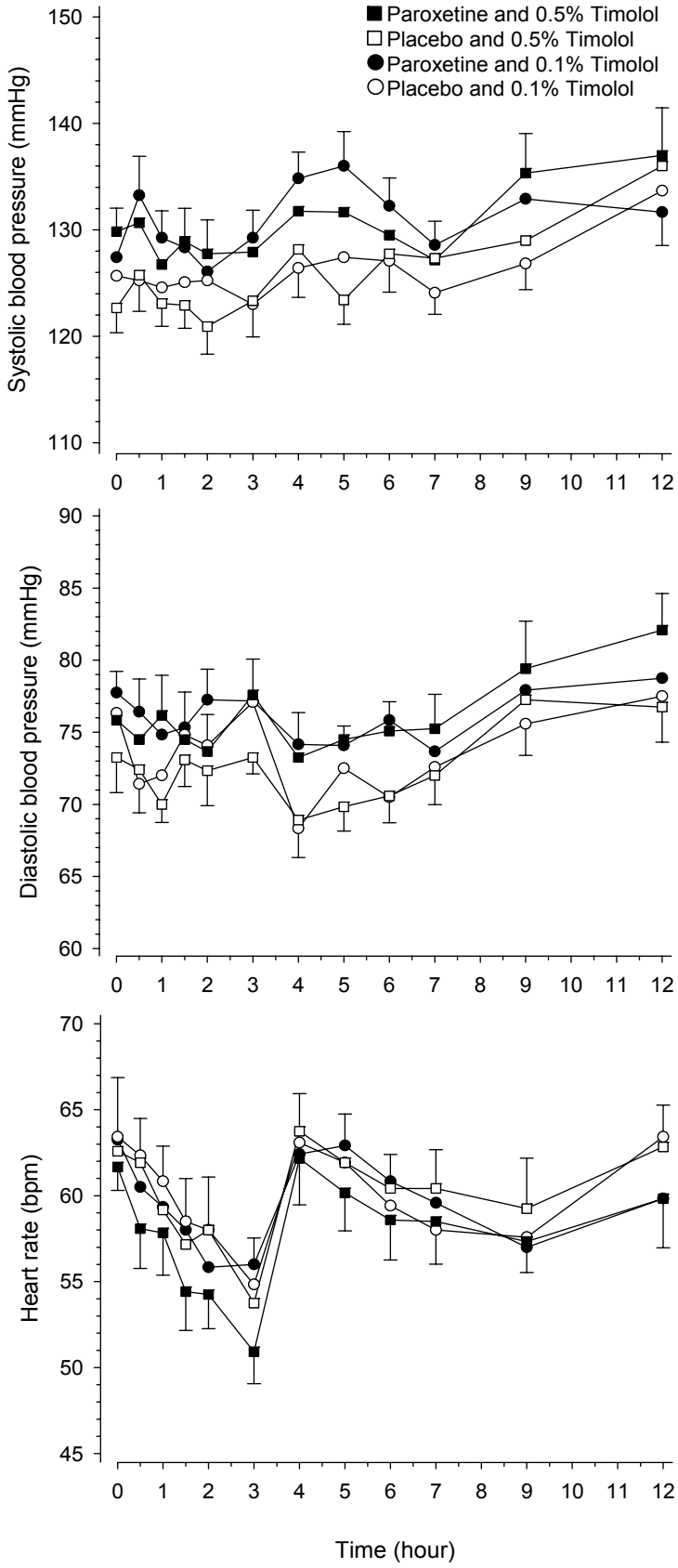
Supplemental Table 1. The baseline and average (0-12 hours) systolic and diastolic blood pressures and heart rate after administration of a single dose of 0.1% eye gel or 0.5% eye drop to both eyes after oral pretreatment with placebo or 20 mg paroxetine daily for 3 days in 12 healthy male volunteers.

Variable	Eye gel 0.1%				Eye drop 0.5%			
	Placebo (control) mean (SD)	Paroxetine mean (SD)	Difference mean (95% CI)	*P*-value	Placebo (control) mean (SD)	Paroxetine mean (SD)	Difference mean (95% CI)	*P*-value
Systolic blood pressure (mmHg)								
Baseline	126 (10)	127 (9)	2 (-3 to 7)	0.45	123 (8)	130 (8)	7 (3 to 11)	0.0031
Average (0-12 h)	127 (8)	131 (8)	5 (1 to 8)	0.012	127 (8)	131 (10)	4 (1 to 7)	0.016
Diastolic blood pressure (mmHg)								
Baseline	76 (8)	78 (5)	1 (-3 to 5)	0.45	73 (8)	76 (5)	3 (-3 to 8)	0.30
Average (0-12 h)	74 (6)	76 (5)	2 (1 to 4)	0.0069	73 (5)	77 (8)	4 (1 to 6)	0.025
Heart rate (bpm)								
Baseline	63 (12)	63 (6)	0 (-7 to 7)	0.96	63 (9)	62 (5)	-1 (-5 to 4)	0.67
Average (0-12 h)	60 (6)	59 (5)	0 (-3 to 2)	0.75	60 (8)	58 (7)	-2 (-4 to -1)	0.011

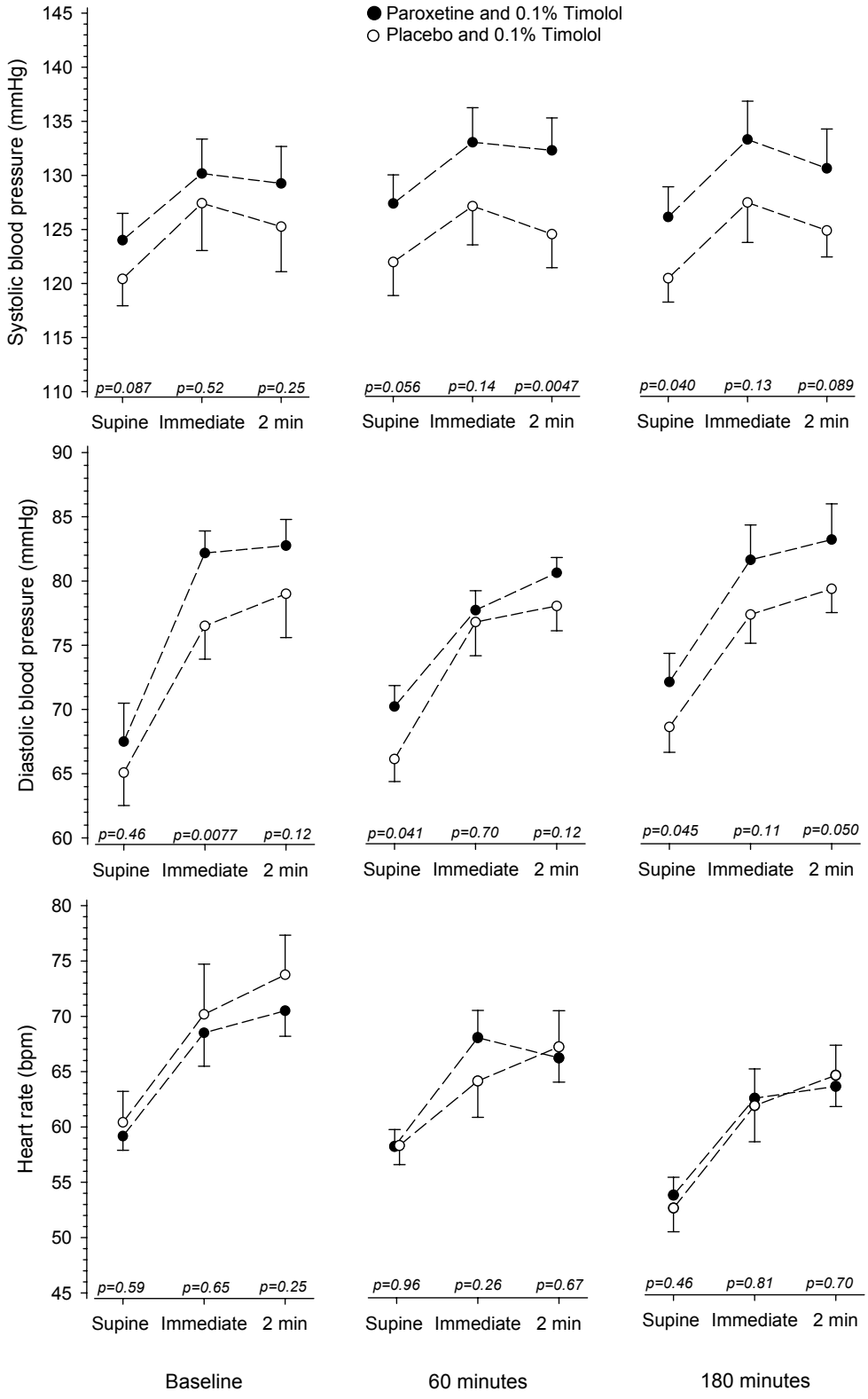
The average values were calculated by dividing the $AUC_{0\text{-}12\ h}$ of the blood pressure or heart rate values by 12 hours.



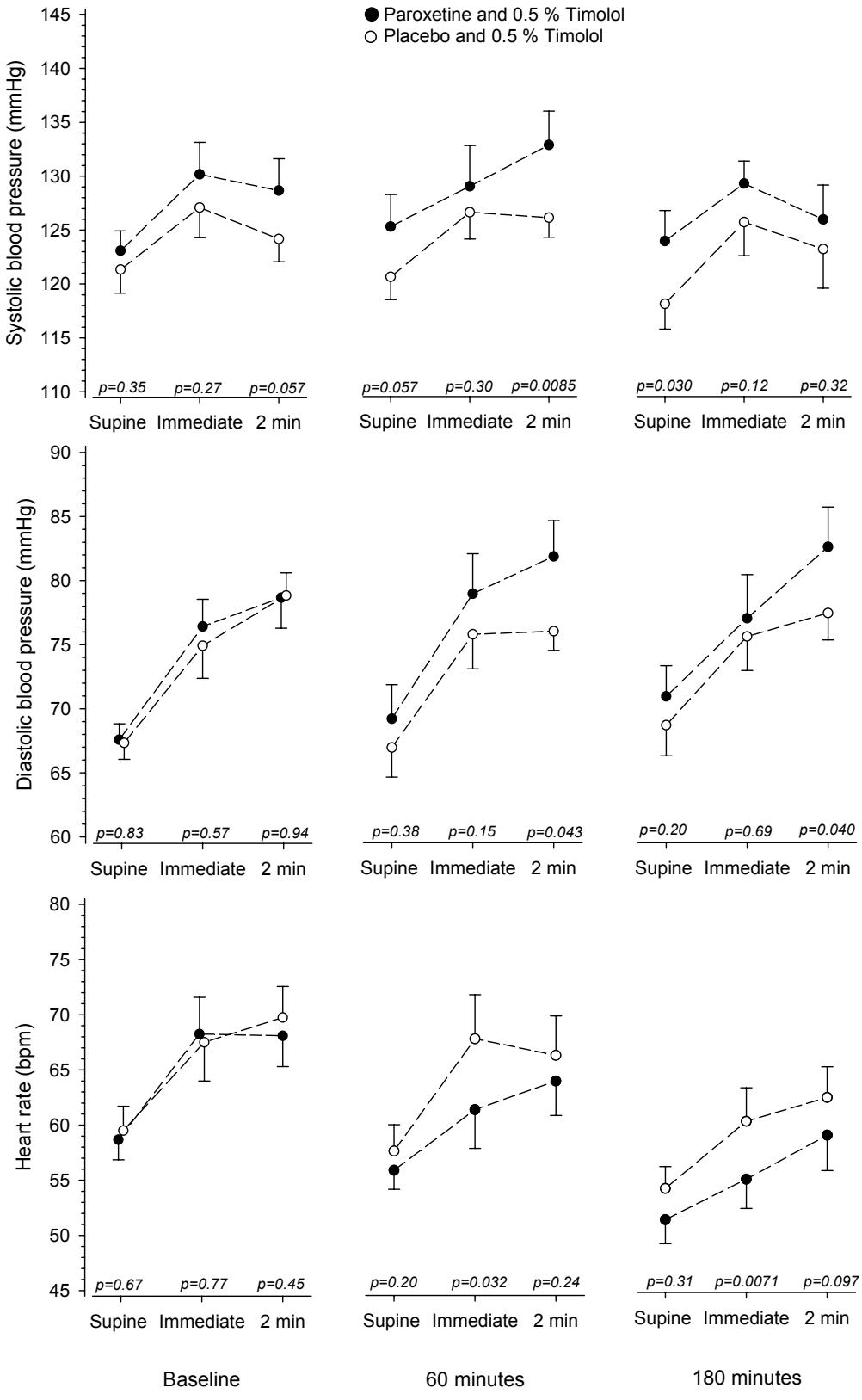
Supplemental Figure 1 The suggested formation routes of timolol metabolites M6 and M7 according to Volotinen et al. (2010). Volotinen M, Korjamo T, Tolonen A, Turpeinen M, Pelkonen O, Hakkola J and Mäenpää J (2010) Effects of selective serotonin reuptake inhibitors on timolol metabolism in human liver microsomes and cryo-preserved hepatocytes. *Basic Clin. Pharmacol. Toxicol.* **106:**302-309.



Supplemental Figure 2 Mean (± standard error) systolic and diastolic blood pressures and heart rate in sitting position after ophthalmic timolol administration in a 4-phase cross-over study in 12 healthy male volunteers. The participants ingested first in a randomized order paroxetine 20 mg or placebo daily for 3 days (phases 1 and 2). On day 3, timolol 0.1% gel was applied on both eyes. During phases 3 and 4, the same 12 participants ingested in randomized fashion paroxetine or placebo, but on day 3, timolol 0.5% aqueous drop was applied on both eyes. Timed measurements continued during each phase up to 12 h after timolol application.



Supplemental Figure 3 Orthostatic test blood pressure and heart rate values in 12 healthy male participants before administration of 0.1% timolol hydrogel and at 60 minutes and 180 minutes postdose during the placebo and paroxetine phases (phases 3 and 4). The 12 participants ingested in a randomized order paroxetine 20 mg or placebo daily for 3 days. On day 3, timolol 0.1% hydrogel was applied on both eyes. Blood pressures and heart rate were measured at rest in supine position, immediately after upright standing and 2 min after upright standing. Mean values and standard errors are shown.



Supplemental Figure 4 Orthostatic test blood pressure and heart rate values in 12 healthy male participants before administration of 0.5% timolol aqueous eye drops and at 60 minutes and 180 minutes postdose during the placebo and paroxetine phases (phases 3 and 4). The 12 participants ingested in a randomized order paroxetine 20 mg or placebo daily for 3 days. On day 3, timolol 0.5% aqueous drop was applied on both eyes. Blood pressures and heart rate were measured at rest in supine position, immediately after upright standing and 2 min after upright standing. Mean values and standard errors are shown.