A phase 1 multiple dose study of tirzepatide in Chinese patients with type 2 diabetes

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Measurement of tirzepatide plasma concentration

The plasma concentration of tirzepatide was evaluated using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS). The HPLC–MS/MS system used was the Triple Quad™ 6500+ (SCIEX) coupled with the LC-30AD series HPLC (Shimadzu Corporation). The analytical column used was the Discovery® BIO Wide Pore C5-3 (5 cm x 1 mm, 3.0 µm; Merck KGaA), with mobile phase A: formic acid:water (5:95); mobile phase B: formic acid:acetonitrile (5:95). The calibration standard range for tirzepatide was 4–500 ng/mL. The PK data were analyzed using standard noncompartmental methods of analysis with the Phoenix WinNonlin Version 8.1 software package (Certara Inc., Princeton, NJ, USA).

Supplementary Table S1. Summary of pharmacokinetic parameters throughout the study in Cohorts 1 and 2.

	Cohort 1			Cohort 2		
Parameter	**Week 0, tirzepatide 2.5 mg (n=10)**	**Week 7, tirzepatide 5.0 mg (n=9)**	**Week 15, tirzepatide 10.0 mg (n=9)**	**Week 0, tirzepatide 2.5 mg (n=10)**	**Week 7, tirzepatide 5.0 mg (n=10)**	**Week 23, tirzepatide 15.0 mg (n=10)**
AUC (0–168) (ng.h/mL)	35100 (14)	125000 (16)	263000 (17)	30900 (14)	110000 (16)	357000 (16)
C_{max} (ng/mL)	306 (28)	1030 (13)	2200 (16)	257 (17)	915 (18)	2930 (20)
T_{max} (h)[1]	24 (8–72)	24 (8–24)	24 (8–48)	23 (8–47)	24 (8–48)	24 (24–24)
$T_{1/2}$ (h)[2]	133 (104–164)	139 (113–226)	132 (113–153)	145 (121–173)	124 (91–170)	126 (114–156)
CL/F (L/h)	0.0384 (17)	0.0399 (16)	0.0381 (17)	0.0428 (17)	0.0454 (16)	0.0420 (16)
Vz/F (L)	7.36 (13)	8.01 (19)	7.23 (11)	8.93 (13)	8.00 (27)	7.61 (13)

Unless otherwise noted, data are expressed as geometric mean (geometric coefficient of variation, in %)

[1]Data are median (minimum–maximum); [2]Data are geometric mean (minimum–maximum)

AUC (0–168), area under the concentration-time curve from zero to 168 hours post-dosing; CL/F, apparent total body clearance calculated after extravascular administration; C_{max}, maximum observed drug concentration; $T_{1/2}$, half-life associated with the terminal rate constant in noncompartmental analysis; T_{max}, time of maximum observed drug concentration; Vz/F, apparent volume of distribution during the terminal phase after extravascular administration.

Supplementary Table S2. Changes from baseline in HbA1c and FPG.

	Placebo (n=4)	Tirzepatide 2.5–10.0 mg (n=10)	Tirzepatide 2.5–15.0 mg (n=10)
HbA1c, %			
Mean baseline[1]	7.8	8.2	7.7
Change at week 16	1.1	−2.4	−1.3
Change at week 24	−0.2	--	−1.6
FPG, mmol/L			
Mean baseline[1]	10.2	10.1	10.2
Change at week 16	0.4	−4.6	−2.6
Change at week 24	−1.4	--	−3.7

FPG, fasting plasma glucose.

[1]Mean absolute value at day 1 pre-dosing.

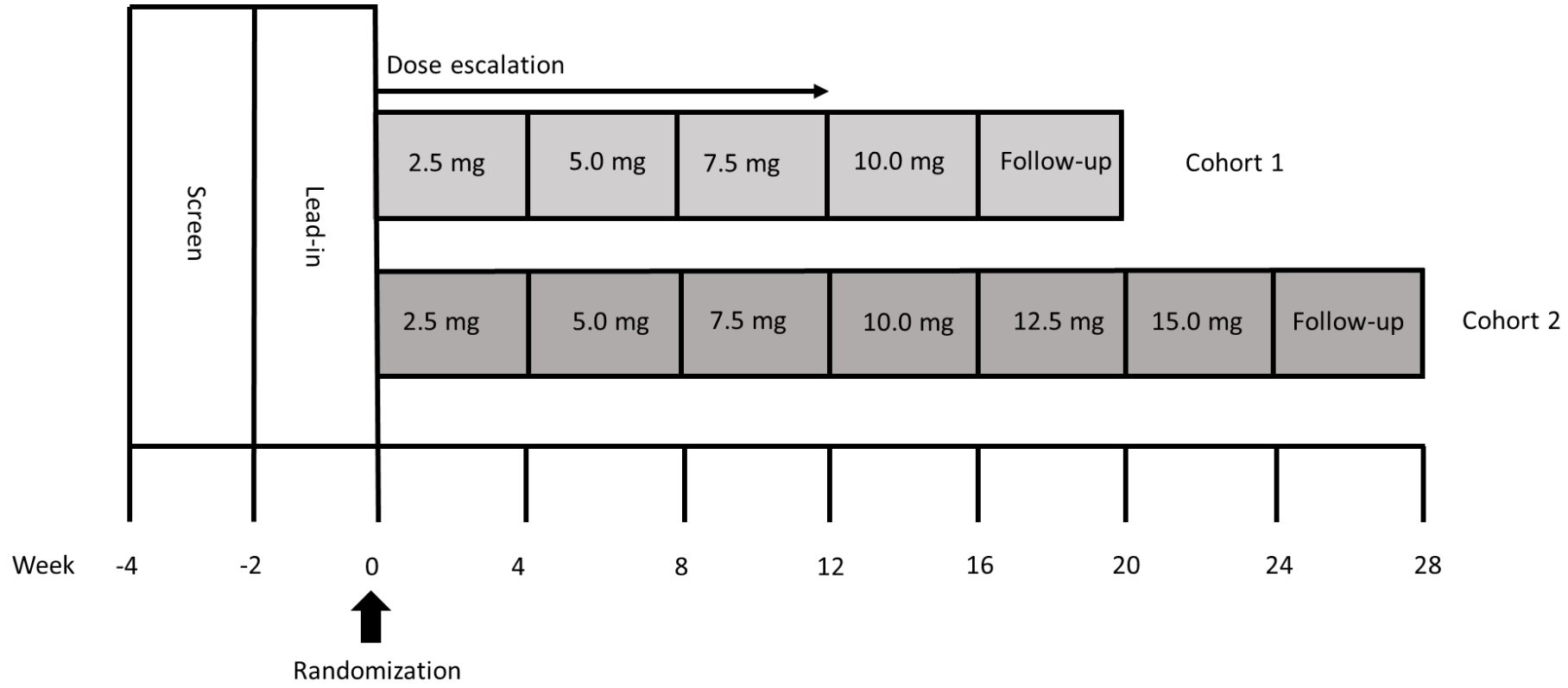
Supplementary Table S3. Changes from baseline in lipid profiles.

	Placebo (n=4)	Tirzepatide 2.5–10.0 mg (n=10)	Tirzepatide 2.5–15.0 mg (n=10)
Total cholesterol, mmol/L			
Baseline[1]	4.89	5.12	4.83
Change at week 16	−0.48	−1.09[2]	−0.74
Change at week 24	−0.33[3]	NA	−0.89
HDL cholesterol, mmol/L			
Baseline	1.02	1.13	1.07
Change at week 16	0.06	0.02	0.02
Change at week 24	0.05[3]	NA	0.02
LDL cholesterol, mmol/L			
Baseline[1]	3.13	2.86	2.96
Change at week 16	−0.28	−0.36[2]	−0.36
Change at week 24	−0.09[3]	NA	−0.59
Triglycerides, mmol/L			
Baseline[1]	2.04	2.61	2.16
Change at week 16	−0.33	−1.54[2]	−0.86
Change at week 24	−0.67[3]	NA	−0.99

HDL, high-density lipoprotein; LDL, low-density lipoprotein

[1]Mean absolute value at day 1 pre-dosing; [2]n=9; [3]n=1

Supplementary Figure S1. Study design.



Within both Cohort 1 and cohort 2 patients were randomized 5:1 to tirzepatide or placebo

Supplementary Figure S2. Summary of meal intake data at baseline and study end.

* End of study data are from day 107 for tirzepatide 2.5-10.0 mg and day 163 for placebo and tirzepatide 2.5-15.0 mg.

Meal intake assessment: Patients were provided standardized lunch and dinner meals with an approximate total energy and macronutrient contents of 700 kCal from 20% protein, 25% fat, and 55% carbohydrate and the meal intake was recorded.