A newly-developed LC-MS method to study possible pharmacokinetic interaction between Linaglptin and Tadalafil upon co-administration in healthy male volunteers

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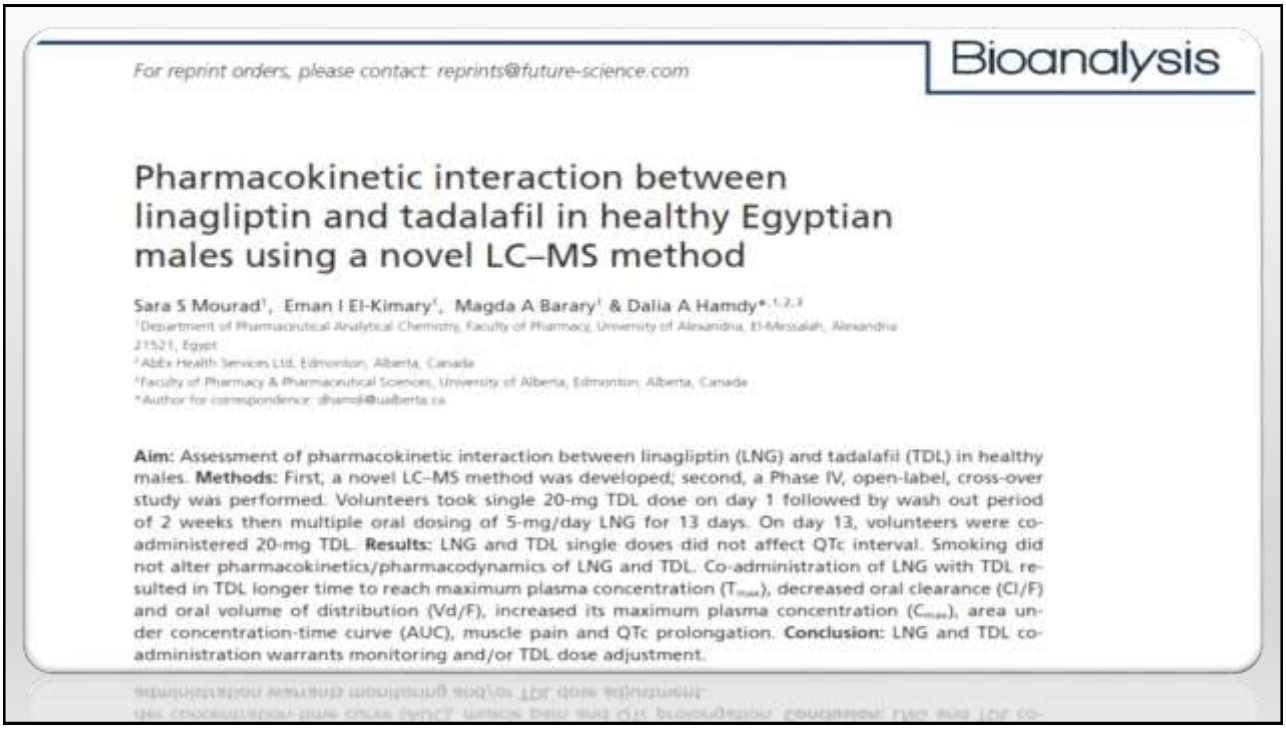

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Bioanalysis

Pharmacokinetic interaction between linagliptin and tadalafil in healthy Egyptian males using a novel LC–MS method

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Aim: Assessment of pharmacokinetic interaction between linagliptin (LNG) and tadalafil (TDL) in healthy males. **Methods:** First, a novel LC–MS method was developed; second, a Phase IV, open-label, cross-over study was performed. Volunteers took single 20-mg TDL dose on day 1 followed by wash out period of 2 weeks then multiple oral dosing of 5-mg/day LNG for 13 days. On day 13, volunteers were co-administered 20-mg TDL. **Results:** LNG and TDL single doses did not affect QTc interval. Smoking did not alter pharmacokinetics/pharmacodynamics of LNG and TDL. Co-administration of LNG with TDL resulted in TDL longer time to reach maximum plasma concentration (T_{max}), decreased oral clearance (Cl/F) and oral volume of distribution (Vd/F), increased its maximum plasma concentration (C_{max}), area under concentration-time curve (AUC), muscle pain and QTc prolongation. **Conclusion:** LNG and TDL co-administration warrants monitoring and/or TDL dose adjustment.

Outline

- Introduction
- Rationale and Objectives
- Methodology
- Results
- Conclusion
- Acknowledgement

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Diabetes Mellitus

- One of the epidemic diseases world-wide and in Egypt
- Chronic hyperglycemia.
- **439** million adults are expected to be diabetic worldwide
- **8.6** million in Egypt in **2030**
- **Tenth** largest population of diabetics
- Microvascular and macrovascular complications.

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Blood Glucose Monitoring

Drugs

Dietary Modification

Regular Medical Care

Glycemic Control & Preventing Complications

Physical Activity

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Diabetes Mellitus-Type 2

Oral Antidaibetics

- Sulfonylureas
- Biguanides
- Alpha-glucosidase inhibitors
- Meglitinides
- Thiazolidinediones
- **Gliptins**

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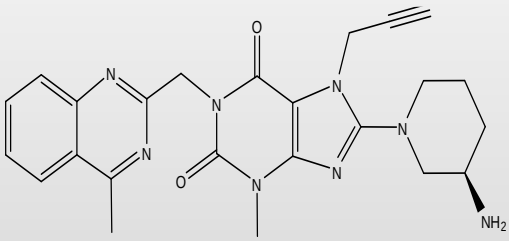
Linagliptin (LNG)



Selective, competitive dipeptidyl peptidase-4 (DPP-4) inhibitors

Recently approved in USA, Japan and Europe for the treatment of type 2 diabetes

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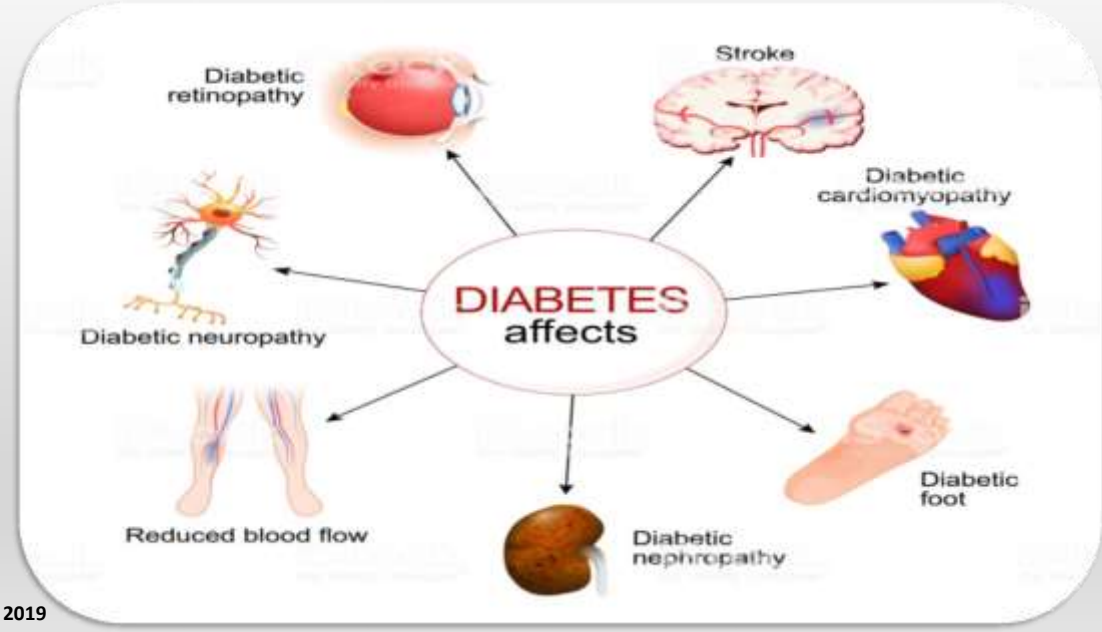
Vascular Complications of DM



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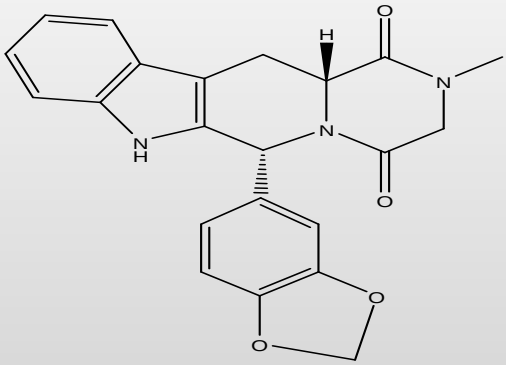
Tadalafil (TDL)



Phosphodiesterase type-5 (PDE-5) inhibitors are common safe drugs for the treatment of erectile dysfunction.

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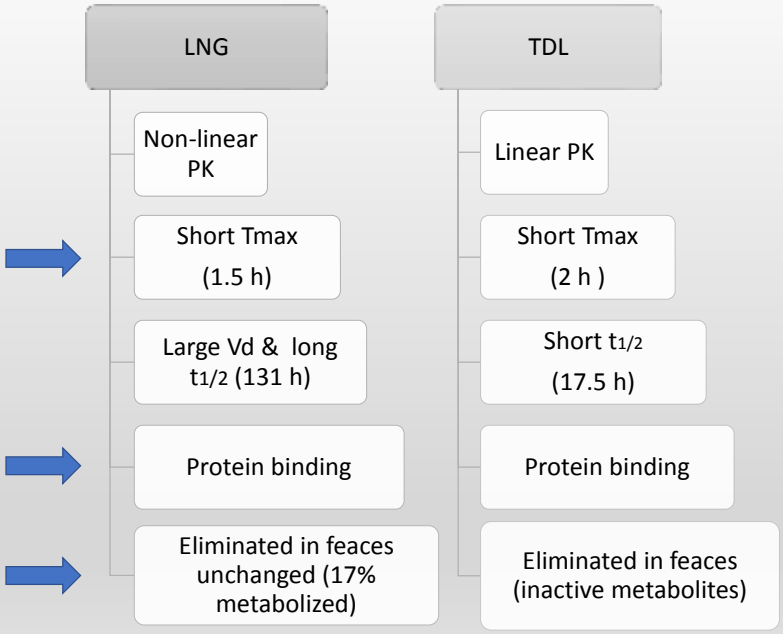

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Aim of the work

- Thus the current work aims to:

1. Develop of a novel, sensitive and reliable LC-MS method for the simultaneous determination of LNG and TDL in human plasma

2. Study the pharmacokinetics and pharmacodynamics of LNG and TDL upon co-administration in healthy Egyptian male volunteers

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Development of LC-MS method for the simultaneous quantitation of Linagliptin and Tadalafil in human plasma

Methodology

Chromatographic Conditions

- Zorbax Eclipse XDB-C18 (4.6 × 150 mm, 5 µm)
- Zorbax Eclipse Plus-C18 guard column (4.6 × 12.5 mm, 5 µm)
- Methanol:0.05 % aqueous formic acid at a gradient elution
- The injection volume was 20 µL
- Flow rate was 1 mL/min
- Run time of 8 minutes
- Shimadzu LC-MS-2020 Single Quadrupole System(positive mode)

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Validation according to US FDA Bioanalytical Method Validation

- **Validation**
  - Linearity
  - LLOD & LLOQ
  - Precision & Accuracy
  - Recovery
  - Selectivity
  - Stability
    - Freeze & thaw
    - Short term
    - Long term
    - Stock solution
    - Autosampler

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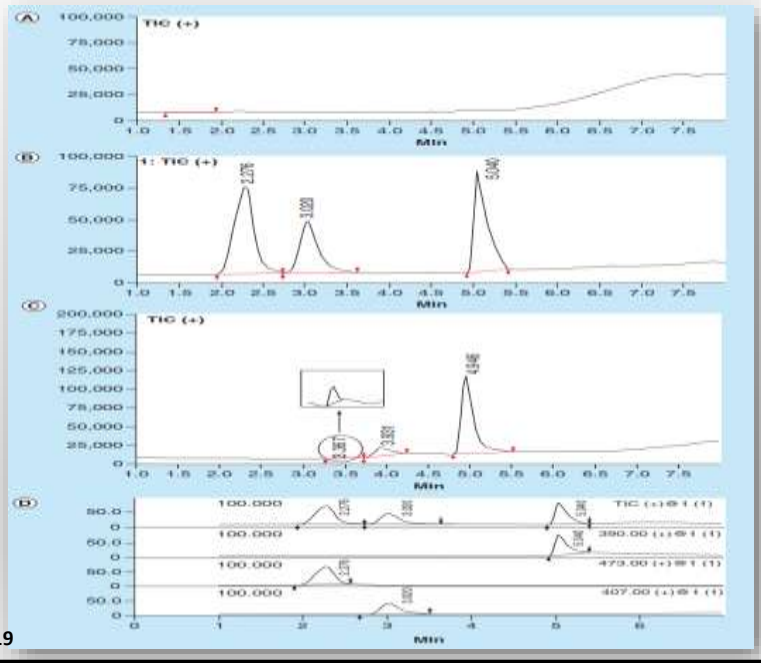
Results

LC-MS Chromatograms



Blank plasma

100 ng/mL LNG, TDL & IS spiked in human plasma

LNG, TDL & IS after 4 h of administration of both tablets

Selected ion monitoring chromatogram

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Results

Characteristic analytical parameters for the proposed LC-MS method for the determination of LNG and TDL in human plasma

Parameters	LNG	TDL
Wavelength of detection (nm)	300	300
m/z $(M+H)^+$	473	390
Linearity range (ng/mL)	1-1000	2-1000
Limit of detection (ng/mL)	0.5	1
Limit of quantitation (ng/mL)	1	2
Intercept	-5.32×10^{-2}	-2.63×10^{-2}
Slope	2.29×10^{-2}	2.22×10^{-2}
Correlation coefficient	0.9999	0.9999
S_a	0.0303	0.0331
S_b	7.64×10^{-5}	8.32×10^{-5}
$S_{y/x}$	7.31×10^{-2}	7.96×10^{-2}
F	90184.35	71161.07
Significance F	9.2×10^{-14}	1.87×10^{-13}

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Studying the possible PK interaction between LNG and TDL in healthy Egyptian males

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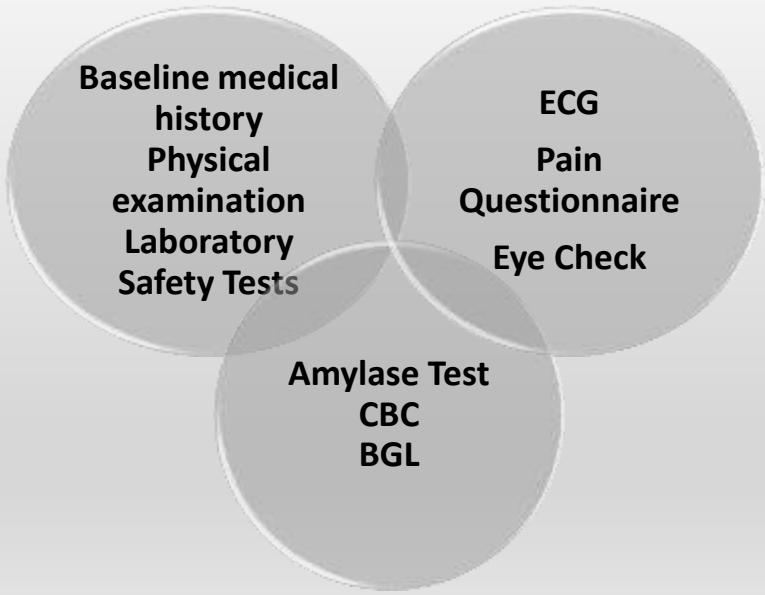
Methodology

Pharmacodynamics/Clinical parameters



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Methodology

Phase IV Open-label Cross-over

Phase I
Day 1: 20 mg tadalafil
Blood sampling at 0.5, 1, 1.5, 3, 4, 6, 8, 12, 24, 48, 72 & 96 h

Wash out period of 2 weeks

Phase II
Day 1: 5 mg linagliptin
Blood sampling at 0.5, 1, 1.5, 3, 4, 6, 8 & 12 h

Phase II
Day 2-12: 5 mg linagliptin
Blood sampling to measure trough concentration (0.5 h predose)

Phase II
Day 13: 5 mg linagliptin + 20 mg tadalafil
Blood sampling at 0.5, 1, 1.5, 3, 4, 6, 8, 12, 24, 48, 72 & 96 h

Plasma separation

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Methodology

Sample Preparation

0.5 mL volunteers' plasma containing LNG &/or TDL

50 µL (1 µg/mL) CVL (IS) + 50 µL 0.3 M NaOH +2 mL ethyl acetate

10 minutes

30 seconds

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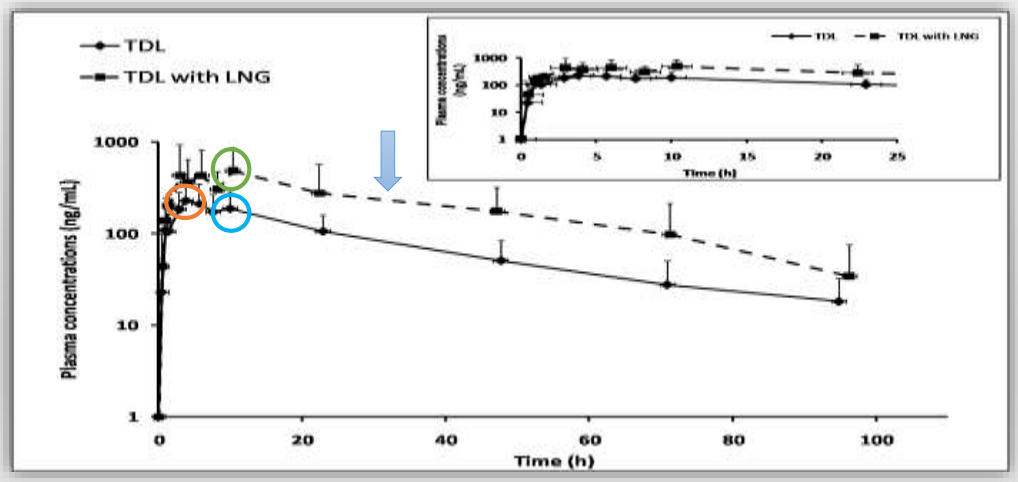
Results

Plasma concentration versus time curve of a 20 mg single dose TDL administered to healthy Egyptian male volunteers alone or after 13 multiple doses of 5 mg/day LNG



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Results

Pharmacokinetics of a 20 mg single dose TDL administered to healthy Egyptian male volunteers alone or after 13 multiple dose of 5 mg/day LNG

PK parameters	TDL	TDL + LNG
Cmax(mg/L)	0.26±0.13	0.66±0.52
Tmax(h)	4.63±2.81	7.83±2.92
$AUC_{0-\infty}$ (mg.h /L)	7.51±3.85	17.7±13.5
$AUC_{0-96\ h}$ (mg.h /L)	6.68±3.14	17.7±13.4
$AUC_{0-24\ h}$ (mg.h /L)	3.46±1.46	8.37±6.08
λz (h^{-1})	0.033±0.018	0.052±0.023
$t_{½}$ (h)	26.30±11.35	14.41±4.76
CL/F (L/h)	3.53±2.14	1.62±1.01
Vd/F(L)	112.00±40.71	35.86±27.36

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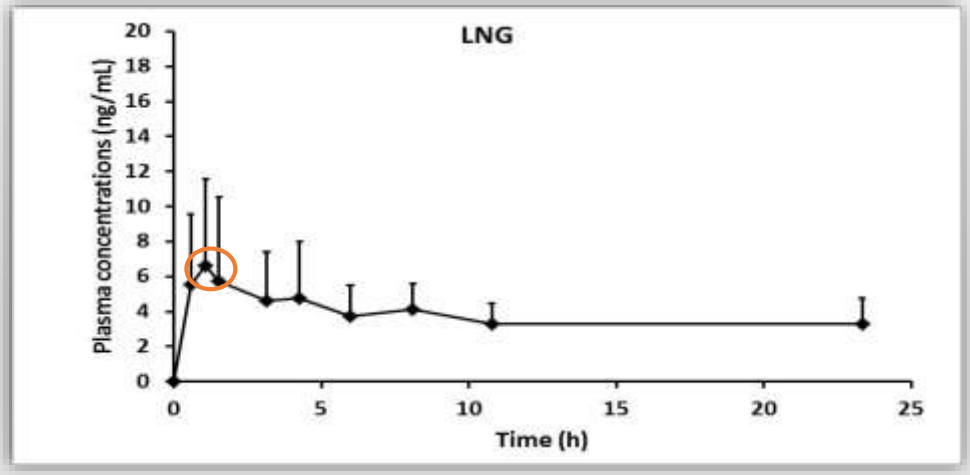
Results

Plasma concentration versus time curve of LNG after single dose administration of 5 mg to healthy Egyptian male volunteers



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Results

Pharmacokinetics of LNG in healthy Egyptian male volunteers after single oral dose of 5 mg

PK parameters	LNG
Cmax (ng/mL)	7.60±4.60
Tmax (h)	2.30±2.75
Cmin (ng/mL)	3.09±1.48
$AUC_{0-\infty}$ (mg.h /L)	0.30±0.12
$AUC_{0-24\ h}$ (mg.h /L)	0.08±0.03
λz (h^{-1})	0.015±0.004
$t_{½}$ (h)	50.46±12.89
CL/F (L/h)	20.24±10.45
Vd/F(L)	1396.49±614.26

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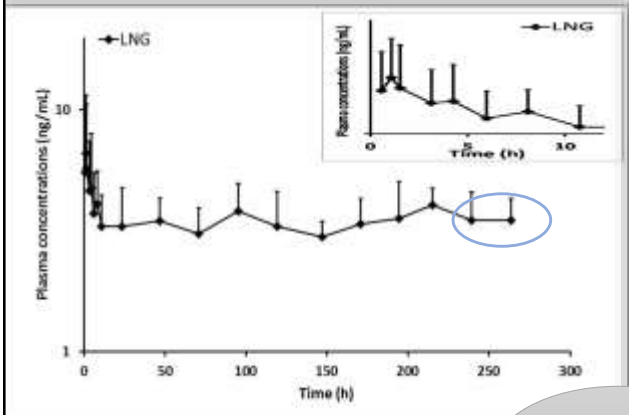
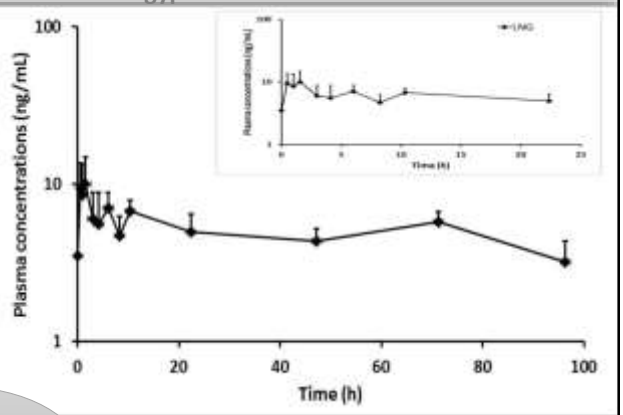
Results

Plasma concentration versus time curve of LNG after multiple dose administration of 5 mg to healthy Egyptian male volunteers for 12 days



Plasma concentration versus time curve of LNG upon co-administration of its 13th dose of 5 mg/day with TDL single dose of 20 mg tablet to healthy Egyptian male volunteers



Cssmin of 3.65±0.72 ng/mL

No Significant Change

Cssmin of 4.54±1.66 ng/mL

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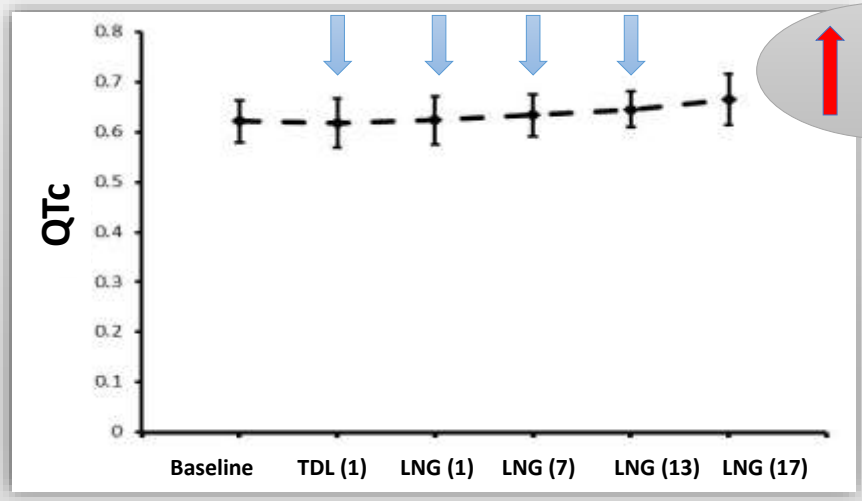
Results

Pharmacodymanics/ Clinical Parameters



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Results

Pharmacokinetics of LNG and TDL after a single oral dose of 5 and 20 mg, respectively, in smokers and non-smoker healthy Egyptian males

PK parameters	TDL		LNG	
	SM	NON-SM	SM	NON-SM
Cmax	0.23±0.11	0.30±0.15	7.68±6.55	7.71±3.65
Tmax (h)	4.75±4.08	4.52±1.02	2.90±3.46	2.16±2.56
Cmin (ng/mL)	-	-	2.71±1.04	3.12±1.02
$AUC_{0-\infty}$ (mg.h /L)	6.54±2.34	8.48±5.05	0.30±0.17	0.29±0.09
$AUC_{0-96\ h}$ (mg.h /L)	5.84±1.95	7.52±4.09	-	-
$AUC_{0-24\ h}$ (mg.h /L)	3.16±1.19	3.75±1.77	0.07±0.04	0.09±0.03
λz (h^{-1})	0.026±0.009	0.040±0.022	0.013±0.003	0.016±0.004
$t_{½}$ (h)	29.73±9.41	22.88±13.12	55.25±12.63	45.68±12.93
CL/F (L/h)	3.37±1.12	3.68±3.00	22.03±14.67	18.45±5.58
Vd/F(L)	134.88±34.71	89.12±34.87	1591.93±765.04	1201.03±439.61

No Significant Difference

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Conclusion

- Both TDL single and LNG multiple dosing were well tolerated by Egyptian healthy volunteers when administered alone
- PK parameters reported in the Egyptian population came in good accordance with those previously reported in Japanese and other Caucasian populations
- Smoking did not affect the PK parameters of any of the drugs in the Egyptian healthy volunteers
- Upon co-administration of both drugs to the volunteers, a drug interaction occurred at the absorption, tissue distribution and elimination levels

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Conclusion

TDL PK & side effects were significantly altered

Tmax

CL (2 folds)

Vd (3 folds)

Cmax & AUC (2.5 folds)

Muscle pain (60%)

QTc prolongation (7%)

Dose adjustment of TDL

Caution & monitoring

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Acknowledgement

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