56 y/o Male
HTN, Dyslipidemia

FBS: 205
HbA1C: 9.5

Plan: 25 mg empagliflozin, 5 mg linagliptin, 1000 mg metformin

Which one do you recommend?

A: Free Combination
B: Fixed Dose Combination

Fixed-dose combination (FDC) drugs benefits:

Improved Patient Compliance

Reduced Pill Burden

Synergistic Effects

Cost-Effectiveness

Wilkins CA, Hamman H, Hamman JH, Steenekamp JH. Fixed-Dose Combination Formulations in Solid Oral Drug Therapy: Advantages, Limitations, and Design Features. Pharmaceutics. 2024 Jan 26;16(2):178. doi: 10.3390/pharmaceutics16020178. PMID: 38399239; PMCID: PMC10892518.

Triple Fixed-Dose Combination of Empagliflozin, Linagliptin, and Metformin for Type 2 Diabetes

Presenter: Seyedeh Zahra Mousavi
Supervisor: Dr. Nasim Ebadati

Objective

Evaluate bioequivalence of a triple fixed-dose combination (FDC) therapy vs. free tablet combinations for Type 2 Diabetes (T2D).

Medications Studied

Empagliflozin (SGLT2 inhibitor), Linagliptin (DPP-4 inhibitor), and Extended-Release Metformin (XR).

Importance

Simplified regimens improve patient adherence and glycemic control.

FDA Approved Doses

	Dose (mg)			
FDC	**Empagliflozin**	**Linagliptin**	**Metformin XR**	**Recommended administration**
1	25	5	1000	One tablet daily
2	12.5	2.5	1000	Two tablets daily
3	10	5	1000	One tablet daily
4	5	2.5	1000	Two tablets daily

Methodology

1. **Study Design**:

   Two open-label, randomized, single-dose, two-period, two-sequence crossover studies.

   Study 1: Compared two FDC tablets (5 mg empagliflozin, 2.5 mg linagliptin, 1000 mg metformin XR) vs. corresponding free combination.

   Study 2: Compared one FDC tablet (25 mg empagliflozin, 5 mg linagliptin, 1000 mg metformin XR) vs. corresponding free combination.

2. **Participant Criteria:**

   Ages 18-55, BMI 18.5-29.9 kg/m^2.

   Excluded: Significant blood pressure issues, relevant diseases, or infections.

Methodology

3. **Endpoints**:
    a. **AUC** (Area Under Plasma Concentration-Time Curve).
    b. **Cmax** (Peak Plasma Concentration).

4. **Statistical Analysis:**
    a. Bioequivalence if geometric mean ratios are within 80-125%.
    b. Sample size determined based on previous trials for sufficient power.

Study Results

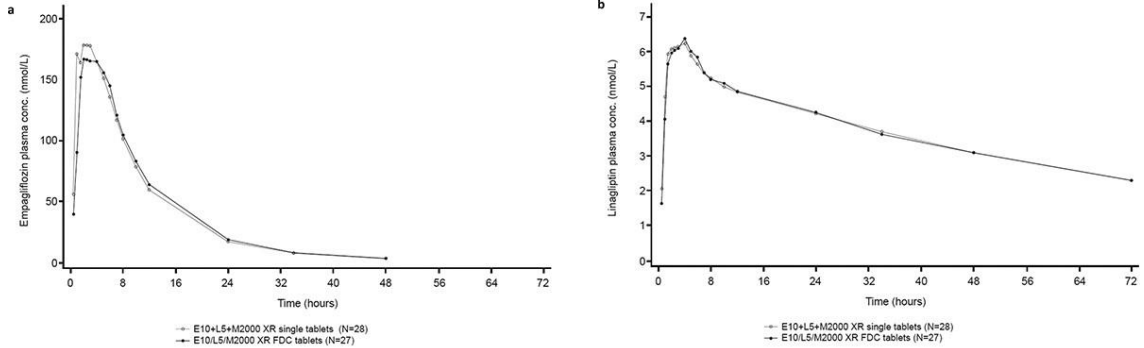
Bioequivalence:

Both FDC doses (low and high) showed bioequivalence to free tablet combinations.

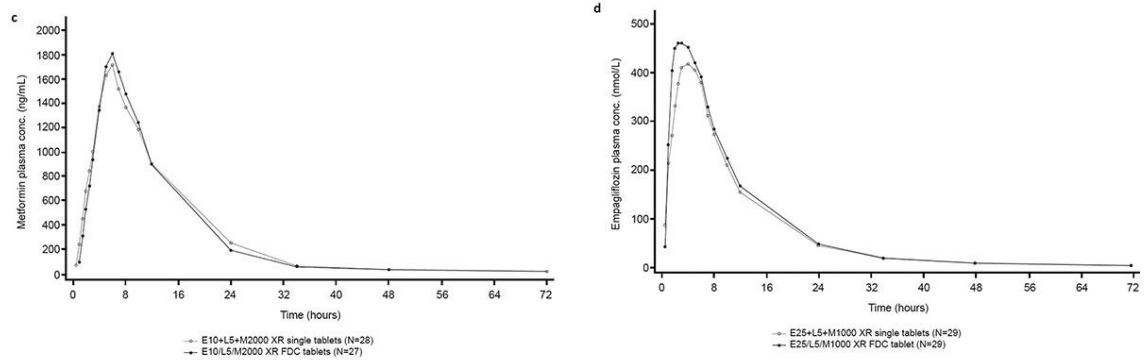
Results within the predefined range (80-125% for AUC and Cmax).

Plasma Profiles:

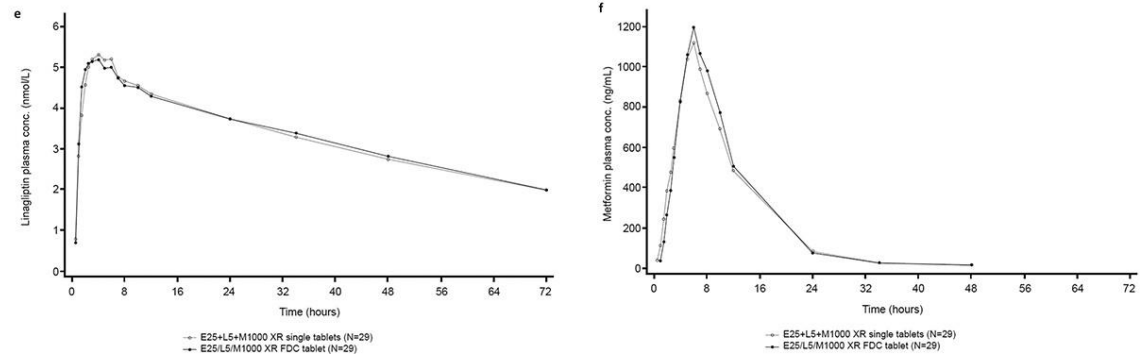
Similar plasma concentration-time profiles for all three drugs in FDC and free combination.


a
Empagliflozin plasma conc. (nmol/L)
Time (hours)
E10+L5+M2000 XR single tablets (N=28)
E10/L5/M2000 XR FDC tablets (N=27)

b
Linagliptin plasma conc. (nmol/L)
Time (hours)
E10+L5+M2000 XR single tablets (N=28)
E10/L5/M2000 XR FDC tablets (N=27)


c
Metformin plasma conc. (ng/mL)
Time (hours)
E10+L5+M2000 XR single tablets (N=28)
E10/L5/M2000 XR FDC tablets (N=27)

d
Empagliflozin plasma conc. (nmol/L)
Time (hours)
E25+L5+M1000 XR single tablets (N=29)
E25/L5/M1000 XR FDC tablet (N=29)


e
Linagliptin plasma conc. (nmol/L)
Time (hours)
E25+L5+M1000 XR single tablets (N=29)
E25/L5/M1000 XR FDC tablet (N=29)

f
Metformin plasma conc. (ng/mL)
Time (hours)
E25+L5+M1000 XR single tablets (N=29)
E25/L5/M1000 XR FDC tablet (N=29)

	Empagliflozin/linagliptin/metformin XR, 2x (5 mg/2.5 mg/1000 mg) (Study 1)		Empagliflozin/linagliptin/metformin XR, 25 mg/5 mg/1000 mg (Study 2)	
	N FDC/Free	Adjusted GMR[a] % (90% CI)	N FDC/Free	Adjusted GMR[a] % (90% CI)
Empagliflozin				
AUC_{0-tz} (nmol*h/L)	27[b]/28[c]	100.42 (98.17, 102.72)	29[d]/29[e]	103.06 (100.36, 105.83)
C_{max} (nmol/L)	27/28	92.57 (85.21, 100.57)	29/29	99.95 (94.52, 105.70)
Linagliptin				
AUC_{0-72} (nmol*h/L)	27/28	100.16 (96.17, 104.31)	29/29	100.31 (96.65, 104.10)
C_{max} (nmol/L)	27/28	97.33 (89.99, 105.26)	29/29	97.17 (92.63, 101.93)
Metformin				
AUC_{0-tz} (ng*h/mL)	27/28	95.34 (91.58, 99.24)	29/29	100.35 (96.11, 104.77)
C_{max} (ng/mL)	27/28	104.83 (98.56, 111.50)	29/29	107.78 (102.52, 113.31)

Safety and Tolerability

Adverse Events (AEs):

No serious adverse events.

AEs included mild/moderate nausea, headache, decreased appetite, and others.

Comparable safety profiles between FDC and free combinations.

	FDC tablet, N (%)	Free combination, N (%)	
	Empagliflozin/linagliptin/metformin XR, 10 mg/5 mg/2000 mg (Study 1)		
Preferred term	**2x (5 mg/2.5 mg/1000 mg) FDC tablets**	**10 mg/5 mg/4x 500 mg free tablets**	**Total**
Number treated	29 (100.0)	30 (100.0)	30 (100.0)
Number with AEs	9 (31.0)	8 (26.7)	14 (46.7)
Number with drug-related AEs	7 (24.1)	6 (20.0)	10 (33.3)
Nausea	4 (13.8)	3 (10.0)	5 (16.7)
Headache	4 (13.8)	2 (6.7)	5 (16.7)
Decreased appetite	1 (3.4)	2 (6.7)	3 (10.0)
Vomiting	1 (3.4)	1 (3.3)	2 (6.7)
Diarrhea	1 (3.4)	1 (3.3)	1 (3.3)
	Empagliflozin/linagliptin/metformin XR, 25 mg/5 mg/1000 mg (Study 2)		
	25 mg/5 mg/1000 mg FDC tablet	25 mg/5 mg/2x 500 mg free tablets	
Number treated	29 (100.0)	29 (100.0)	30 (100.0)
Number with AEs	14 (48.3)	7 (24.1)	17 (56.7)
Number with drug-related AEs	6 (20.7)	4 (13.8)	9 (30.0)

Conclusion

FDA Approval: Based on the studies, the FDA approved the triple FDC for T2D.

Benefits:

- Simplifies treatment regimen.
- Improves adherence and glycemic control.

Clinical Impact: Supports the use of this FDC as a convenient option for patients requiring multiple glucose-lowering therapies.

Key Benefits of FDC Therapy

Improved Adherence: Fewer pills make it easier for patients to stick to their treatment plans.

Patient Satisfaction: Simpler regimens can increase satisfaction.

Lower Risk of Complications: Better adherence can lead to reduced long-term risks of T2D-related complications.

Summary of Findings

- FDC of empagliflozin, linagliptin, and metformin XR is **bioequivalent** to separate tablets.
- **Safe and well-tolerated** in healthy volunteers.
- **Potential for improved adherence** and outcomes in patients with T2D.

References

- **Source**: Lingvay et al. (2020). Postgraduate Medicine, 132:4, 337-345.
- **DOI**: https://doi.org/10.1080/00325481.2020.1750228