A Study to Evaluate the Pharmacokinetics and Taste Profile of a Prototype Orally Disintegrating Tablet Formulation For MK-0663

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INTRODUCTION & OBJECTIVES

Arcoxia® (MK-0663, etoricoxib) is a selective inhibitor of cyclooxygenase-2 (COX-2), indicated for the treatment of symptomatic relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, inflammation associated with acute gouty arthritis, and acute and chronic pain. Currently available as a film-coated tablet (FCT), an orally disintegrating tablet (ODT) formulation was developed for those with difficulties swallowing a tablet.

This study had the following objectives:

- To compare the bioavailability between a single dose administration of the ODT (120 mg) and the reference FCT of Arcoxia® (120 mg) with and without water in healthy subjects.

- To assess taste attributes (including bitterness) of the formulation with varying levels of taste masking excipients at 60, 90 and 120 mg of MK-0663.

STUDY DESIGN & TREATMENTS

This was a 2-part, single-center study conducted in 15 healthy subjects. Subjects (18-55 years of age, and BMI of 18.0-30.0 kg/m^2, inclusive) participated in both Parts I and II.

- **Part I**: a single-dose, open-label, randomized, 3-way crossover oral biocomparison study
- **Part II**: a single-dose, open-label, randomized, crossover study to evaluate the taste of the taste-masked ODT formulations of MK-0663.

Part I Treatments:

A*	Single-dose, oral administration of 120 mg MK-0663 ODT placed on the tongue to dissolve after 20 mL of water under fasting conditions
B	Single-dose, oral administration of 120 mg MK- 0663 ODT swallowed with 240 mL of water under fasting conditions
C	Single-dose, oral administration of 120 mg MK-0663 as a film-coated tablet (Arcoxia®) swallowed with 240 mL of water under fasting conditions

* To evaluate taste and aftertaste, subjects who received MK-0663 ODT during Treatment A also received 2 probe samples (at least 1 h pre-dose and 2 h postdose) of a reference compound (1 and 2 mg/mL caffeine solution, respectively).

Part II Treatments:

	MK-0663 Dose for Taste testing **	Sucralose	Neotame	Peppermint
D	1 mL suspension consisting of **60** mg MK-0663	2.5 mg	0.1 mg	5 mg
E	1 mL suspension, consisting of **60** mg MK-0663	10 mg	0.2 mg	10 mg
F	1.5 mL suspension, consisting of **90** mg MK-0663	3.75 mg	0.15 mg	7.5 mg
G	1.5 mL suspension, consisting of **90** mg MK-0663	15 mg	0.3 mg	15 mg
H	2 mL suspension, consisting of **120** mg MK-0663	5 mg	0.2 mg	10 mg
I	2 mL suspension, consisting of **120** mg MK-0663	20 mg	0.4 mg	20 mg

** The samples were retained in the mouth for 10 seconds, expectorated and the taste attributes were collected and captured in the questionnaires.

RESULTS

Fifteen (15) healthy subjects (7 males and 8 females) were randomized and all subjects completed both Parts I and II of the study.

Fig 1. The Arithmetic Mean of the MK-0663 Plasma Concentration – Time Profiles Following a Single Oral Administrations of Treatments A, B, and C are presented below:

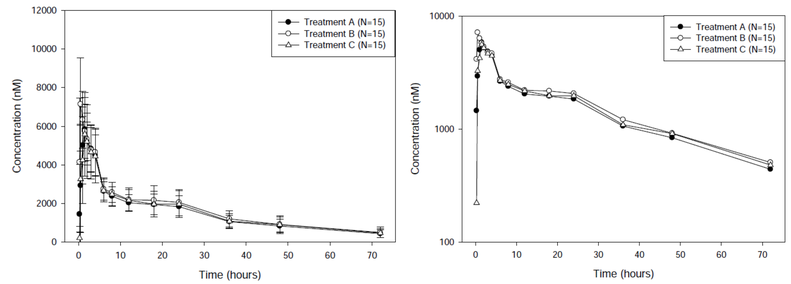

Table 1. A Summary of the PK Evaluation of Plasma MK-0663 Following Administration of Treatments A, B and C in Healthy Subjects under Fasting conditions

	Treatment A	Treatment B	Treatment C	A/B	A/C	B/C
PK parameter	GM ± 95% CI	GM ± 95% CI	GM ± 95% CI	GMR ± 90% CI	GMR ± 90% CI	GMR ± 90% CI
C_{max} (nM)	6991.16 (6096.59, 8017.00)	7529.78 (6623.83, 8559.65)	6088.10 (4920.81, 7532.28)	0.93 (0.81, 1.06)	1.15 (1.01, 1.31)	1.24 (1.07, 1.43)
$AUC_{0\text{-}last}$ (h.µM)	102.49 (90.37, 116.24)	112.88 (97.28, 130.98)	104.20 (88.87, 122.17)	0.91 (0.85, 0.97)	0.98 (0.92, 1.05)	1.08 (1.05, 1.11)
$AUC_{0\text{-}inf}$ (h.µM)[1]	120 (28,6)	133 (34.5)	124 (34.0)			
T_{max} (h)[2]	1.00 (0.25, 3.00)	0.50 (0.25, 2.00)	1.50 (0.50, 12.00)			
$t_{½}$ (h)[1]	26.6 (24.1)	25.8 (39.3)	27.9 (30.4)			

[1] Geometric mean and percent of geometric coefficient of variation reported for $AUC_{0\text{-}inf}$ and $t_{1/2}$;
[2] Median (min, max) reported for t_{max}

Table 2. Bitterness Assessment Following Reference (1 mg/mL caffeine) and Treatment A:

		minutes after ODT dosing									
	reference	0.5	1	5	10	20	30	45	60	90	120
very strong		6	4	2	1						
strong	1	9	11	10	4	2	2				
moderate	6			3	8	9	5	5	1		
weak	7				2	4	8	9	10	4	3
not present	1							1	4	11	12

Bitterness of ODT tablet compared to first reference product

More bitter	14
Less bitter	1

Taste of ODT tablet

No specific taste	2
Bitter	13
Metallic	1

Mouth feeling caused by ODT tablet

No specific feeling	9
Stinging	3
Numbing	1
Irritating	1
Something else	3

General taste of ODT tablet

Neutral	1
Not tasty	4
Awful	10

Bitterness of ODT tablet compared to second reference sample

More bitter	9
Less bitter	6

Table 3. Part II: Taste Assessment – Bitterness (intensity)

	1 min						5 min						10 min						20 min					
	D	E	F	G	H	I	D	E	F	G	H	I	D	E	F	G	H	I	D	E	F	G	H	I
very strong	1	1			1		2																	
strong	8	5	7	2	2	3	3	2	3	4	4	3	3	2	3	1	3	2	1	1	1		1	
moderate	4	4	2	4	7	6	9	9	6	5	6	6	7	4	4	5	3	5	4	2	3	3	4	5
weak	2	4	3	5	4	3	1	3	5	5	5	2	5	8	7	6	8	5	10	10	9	7	9	5
not present		1	2	1	1	3		1	1	1		4		1	1	3	1	3		2	2	5	1	5

	30 min						60 min						90 min						120 min					
	D	E	F	G	H	I	D	E	F	G	H	I	D	E	F	G	H	I	D	E	F	G	H	I
very strong																								
strong	1						1																	
moderate	3	3	1	1	4	2	1	1		1	1					1								
weak	8	7	7	8	5	7	6	4	2	3	5	5	6	2	2	1	2	1	3	1			2	
not present	3	5	7	6	6	6	7	10	13	11	9	10	9	13	13	14	12	14	12	14	15	15	13	15

Table 4. Part II: Taste Assessment – Acceptability and Bitterness best masked

	Is given formulation acceptable or not as medication from taste perspective						In which of the two formulations was the bitterness best masked?					
	D	E	F	G	H	I	DE	ED	FG	GF	HI	IH
Extremely acceptable	1	2	6	5	4	7						
Acceptable	7	12	8	10	9	8						
Barely acceptable	5		1		1							
Unacceptable	2	1			1							
No difference								1		1	1	1
The first formulation							1	4	1	1		2
The second formulation							6	3	6	6	7	4

CONCLUSIONS

- **Part I -** the highest strength of 120 mg (unmasked) demonstrated that unsweetened and unflavored ODT probe has a long-lasting bitter taste
  - **PK** - Single oral doses of 120 mg MK-0663 ODT administered with and without water were bioequivalent (for AUC, not Cmax)
  - Specifically, the extent of absorption of MK-0663 in 120 mg MK-0663 ODT administered with and without water is bioequivalent to the 120 mg MK-0663 FCT administered with water.
  - The rate of absorption appears to be faster with ODT compared to the FCT.

- **Part II** – Based on taste and intensity assessments questionnaire, the responses were favorable to the high excipient formulations, especially at the higher strengths of 90 mg and 120 mg (but not so clear at 60 mg), hence masking was effective in blocking the bitterness.

- All treatments were well tolerated.