Supratherapeutic Dose of Metoclopramide Nasal Spray Shown to Have No ECG Effects in Healthy Male and Female Volunteers: Results of the First Metoclopramide Thorough ECG Study

Marilyn R. Carlson, DMD, MD; Wayne M. Alves, PhD, Evoke Pharma, Inc., Solana Beach, California; Jay W. Mason, MD, University of Utah, Salt Lake City, Utah

Background

Metoclopramide, the only FDA-approved drug for gastroparesis, is widely used by patients with multiple medical conditions, such as diabetes, that put them at increased risk for cardiac events. Since metoclopramide tablets and injection were approved in 1980, there have been very few reports of torsades de pointes, cardiac arrest, and/or sudden death associated with the use of the FDA-approved doses of the oral formulation. Literature reports of cardiac events are primarily associated with parenteral administration in patients who are medically compromised, but there has been a lack of definitive information for prescribing physicians regarding the effects of metoclopramide on the QT interval.

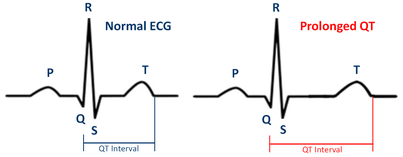
Evoke Pharma is developing a nasal spray formulation of metoclopramide (EVK-001) for patients with acute or recurrent symptoms of diabetic gastroparesis and performed the first metoclopramide thorough electrocardiogram (ECG) study.

The to-be-marketed dose of EVK-001 is 10 mg used 30 minutes before meals and at bedtime.

EVK-001

Design of TQT Studies

- Thorough ECG (TQT) studies are designed to confidently exclude that a drug prolongs the QTc interval 10 milliseconds (ms) or more at the one-sided upper 95% confidence limit
- Drugs with a positive TQT study (i.e., cannot exclude effect >10 ms) need additional ECG monitoring
- Moxifloxacin, a fluoroquinolone antibiotic with a mild QT prolonging effect, is often used as the positive control
- A therapeutic dose and a supratherapeutic dose of the drug being investigated are compared to moxifloxacin



Objectives

- Primary: To define the QT/QTc effects of supratherapeutic dose of EVK-001 administered to healthy adult male and female subjects
- Secondary: To define the ECG effects of a therapeutic dose of EVK-001 and to assess assay sensitivity with an active control, moxifloxacin
- Other: Evaluate the safety and pharmacokinetics of both doses of EVK-001

ECG Methods

- Three ECGs were extracted approximately 1 minute apart before dosing (0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing
- After dosing, subjects were monitored for 24 hours using a continuous 12-lead ECG telemetry system

ECG Endpoint Calculations

- **QTcF** - Fridericia's Correction Formula - A formula which takes into account the physiologic shortening of the QT interval which occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates
- **dQTcF** - Time-matched pre-dose adjusted difference in QTcF at each post-dose time point
- **ddQTcF** - Endpoint defined for each subject in the therapeutic, supratherapeutic and moxifloxacin treatment arms as dQTcF minus the dQTcF during placebo treatment at each post-dose time point

Study Methods

- This was a randomized, double-blind, double-dummy, single-site, 4-period crossover study in healthy male and female subjects
- Subjects each received a study treatment on days 1, 5, 9, and 13, under fasted conditions
- To achieve the steady state exposure of EVK-001, 20 mg was selected as the "therapeutic" dose
- Study Treatments Administered
  - **A** - Metoclopramide therapeutic dose:
    two 10 mg metoclopramide nasal sprays (20 mg), six placebo nasal sprays, one placebo capsule
  - **B** - Metoclopramide supratherapeutic dose:
    eight 10 mg metoclopramide nasal sprays (80 mg), one placebo capsule
  - **C** - Placebo:
    eight placebo nasal sprays, one placebo capsule
  - **D** - Moxifloxacin:
    eight placebo nasal sprays, one 400 mg moxifloxacin tablet

Subject Demographics

		Treatment [a]				
	Parameter	Sequence 1: ABDC (n = 12)	Sequence 2: BCAD (n = 12)	Sequence 3: CDBA (n = 12)	Sequence 4: DACB (n = 12)	Overall (N = 48)
Age (years)	Mean (SD)	34.1 (11.94)	38.9 (6.68)	33.4 (7.60)	35.2 (10.09)	35.4 (9.26)
	Min, Max	21, 54	29, 50	21, 47	20, 52	20, 54
BMI (kg/m^2)	Mean (SD)	26.92 (3.315)	27.08 (3.288)	24.17 (2.250)	27.33 (3.962)	26.38 (3.412)
	Min, Max	22.0, 33.0	21.0, 33.0	21.0, 28.0	18.0, 32.0	18.0, 33.0
Sex, n%	Female	6 (50.0)	6 (50.0)	6 (50.0)	6 (50.0)	24 (50.0)
	Male	6 (50.0)	6 (50.0)	6 (50.0)	6 (50.0)	24 (50.0)
Race, n%	Asian	0	0	1 (8.3)	0	1 (2.1)
	Black or African American	3 (25.0)	5 (41.7)	3 (25.0)	4 (33.3)	15 (31.3)
	White	9 (75.0)	7 (58.3)	8 (66.7)	8 (66.7)	32 (66.7)
Ethnicity, n%	Hispanic or Latino	5 (41.7)	1 (8.3)	2 (16.7)	0	8 (16.7)
	Not Hispanic or Latino	7 (58.3)	11 (92.7)	10 (83.3)	12 (100.0)	40 (83.3)

[a]Treatment A: EVK-001 (20 mg), Treatment B: EVK-001 (80 mg), Treatment C: Placebo, Treatment D: Moxifloxacin 400 mg

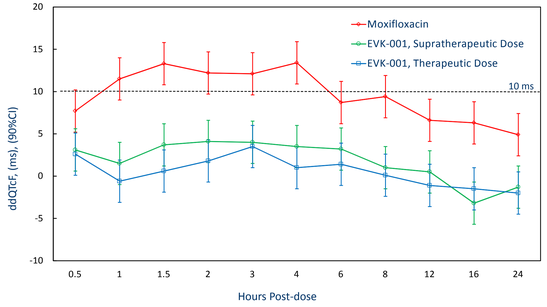
- **Demographics**
  - Forty-eight subjects were enrolled and randomly assigned to a treatment sequence
  - Average age: 35.4 years
  - Sex: 24 males and 24 females
  - 66.7 % Caucasian and 83.3% Not Hispanic or Latino

Safety

Study Treatment	% of Subjects with at least 1 TEAE	% TEAE's Reported by 2 or more subjects
EVK-001, 20 mg	10.4%	dysgeusia 6.3%
EVK-001, 80 mg	20.8%	diarrhea 4.2% headache 4.2%
Placebo	8.3%	headache 6.3%
Moxifloxacin, 400 mg	14.6%	nausea and vomiting symptoms 10.4% headache 4.2%

- **Safety**
  - All 48 subjects completed all four treatment periods and there were no serious adverse events (SAEs)
  - All AEs were mild in severity with the exception of one report of abdominal pain after dosing with moxifloxacin which was assessed as moderate in intensity

ddQTcF (ms) for EVK-001 and Moxifloxacin



ECG Results

- EVK-001 did not increase QTcF or demonstrate consistent ECG changes at an 80 mg supratherapeutic dose and a 20 mg dose
- The active control, Moxifloxacin, performed as expected
- There was no consistent or clinically significant change in HR, PR, or QRS interval associated with any of the treatments

Conclusions

- These negative ECG results for EVK-001 at the supratherapeutic dose (8 times the to-be-marketed dose) will provide useful clinical information for prescribing physicians and their patients with acute or recurrent symptoms of diabetic gastroparesis
- Both doses of EVK-001 were well-tolerated by the healthy male and female subjects in this study
- EVK-001 is being developed for patients with acute or recurrent symptoms of diabetic gastroparesis