P3.257

Impact of Delayed-Dose Administration of USL255, Qudexy™ XR (Topiramate) Extended-Release Capsules

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INTRODUCTION

- Despite the importance of medication adherence for successful management of seizure disorders, nonadherence continues to be a significant problem in patients with epilepsy[1]
- Nonadherence to treatment, including delayed or missed antiepileptic drug (AED) dosing, can lead to increased seizure occurrence, reduced quality of life, frequent hospitalization and emergency room visits, and higher rates of morbidity/mortality[1-3]
- As use of extended-release (XR) AEDs has been shown to improve drug adherence,[4] Upsher-Smith Laboratories, Inc. developed USL255, Qudexy™ XR (topiramate) extended-release capsules, as a once-daily (QD) treatment for epilepsy[5]
  - USL255 was approved by the FDA (11 March 2014) as initial monotherapy for partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures (patients aged ≥10 years) and adjunctive therapy for POS, PGTC, or seizures associated with Lennox-Gastaut syndrome (patients aged ≥2 years)[5]
  - The efficacy and safety of USL255 as adjunctive treatment for POS was recently evaluated in a multinational phase 3 study (PREVAIL; NCT01142193)[6]
- Delayed administration of XR AEDs, taken less frequently than immediate-release formulations, may lead to a decrease in plasma concentrations from steady-state values to below minimum therapeutic concentrations[4]
- The objective of these analyses was to predict the impact of delayed-dose administration of USL255 QD (taken 6, 12, 18, or 24 hours later than scheduled) in a simulated steady-state pharmacokinetic (PK) profile

METHODS

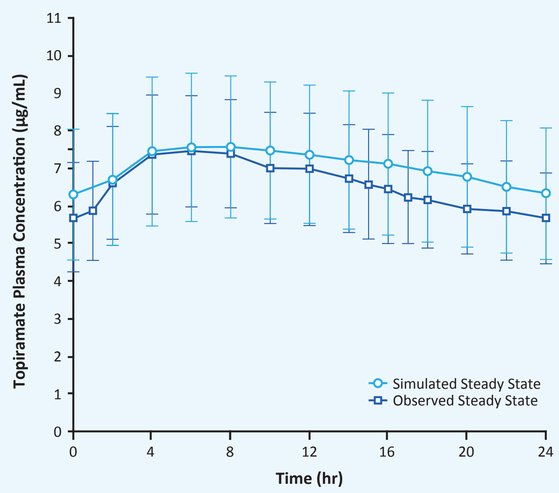
- Data for these post hoc analyses were obtained from a phase 1, open-label, single-dose study evaluating the PK profile of USL255 200 mg administered in the fasted state to 36 healthy adults (age 18 – 65 years)[7]
- Blood samples were drawn within 1 hour pre-dose (0 hr), every 2 hours up to 32 hours post-dose, and at 36, 48, 72, 96, 120, 168, 216, 264, and 336 hours post-dose
- Using the single-dose data, nonparametric superpositioning was used to predict steady-state PK profiles of USL255 200 mg/day
- Compliant dosing of USL255 QD administration for 14 days was utilized to achieve simulated steady-state conditions
- After 14 days of simulated compliant dosing, a 6-, 12-, 18-, and 24-hour delay in USL255 administration was simulated, with QD dosing resuming after the late dose
  - For the 24-hour delay, two doses were assumed to be taken together (ie, double dose)
- Mean-predicted concentrations were calculated for each delayed-dose scenario then compared with steady-state concentrations without a delayed dose (compliant dosing)
- Simulated minimum and maximum plasma concentrations (C_{min} and C_{max}) were evaluated for up to 96 hours following the late dose, and the magnitude of change after administration of the delayed dose was compared with compliant dosing

RESULTS

Simulation of Mean-Predicted Steady-State Plasma Concentrations

- Steady-state conditions were reached within 14 days of simulated dosing of USL255 200 mg/day
- The mean steady-state profile obtained from superpositioning single-dose data was visually similar to the mean steady-state profile obtained from a separate study evaluating USL255 200 mg administered QD for 14 days[8] (Figure 1), thus supporting the appropriateness of simulation methodology to predict steady-state topiramate levels

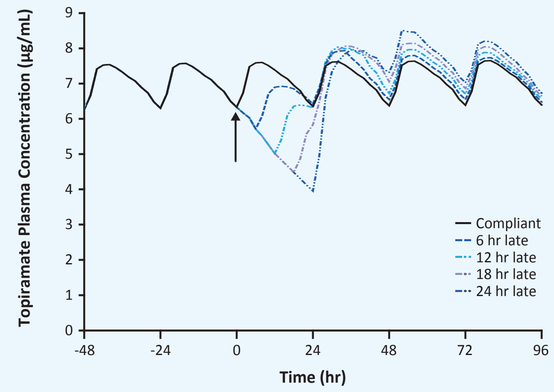
Figure 1. Comparison of Day 14 Mean Steady-State Profiles (Obtained from Superpositioning Single-Dose Data) With Observed Multiple Dosing of USL255 200 mg QD



Simulation of a Delayed USL255 Dose

- Following administration of USL255 6, 12, 18, or 24 hours later than scheduled, mean-predicted topiramate plasma concentrations incrementally decreased prior to the next scheduled dose compared with plasma concentrations resulting from compliant dosing of USL255 200 mg/day (Figure 2)
- Within one 24-hour dosing interval after the late dose, predicted topiramate concentration-time profiles for all 4 delayed-dose scenarios were similar by visual comparison to simulated steady-state concentrations with full compliance (Figure 2)

Figure 2. Comparison Between Mean-Predicted Steady-State Profile of USL255 200 QD (Compliant Dosing) and Mean-Predicted Delayed-Dose Administration of USL255



Arrow indicates when the scheduled dose was to occur for delayed-dose scenarios.

Changes in Predicted Minimum and Maximum Topiramate Plasma Concentrations After Delayed USL255 Dosing

- Compared with compliant dosing, both C_{min} and C_{max} values were increased up to 3 days after the late dose (Figure 2 [24 – 96 hr]; Table 1)
- Topiramate plasma concentrations were highest between 1 and 2 days after a delayed dose of USL255 (Figure 2 [24 – 72 hr]; Table 1)
- Within 1 day after delayed-dose administration, C_{min} values for all delayed-dose scenarios were at or above the steady-state C_{min} levels with compliant dosing (Figure 2)
  - Topiramate plasma concentrations returned to at least steady-state C_{min} levels approximately 4, 6, 8, and 4 hours after USL255 was administered 6, 12, 18, and 24 hours late, respectively
- C_{max} did not increase to more than 10% above compliant dosing for the 6, 12, or 18 hour delayed-dose scenarios (Table 1)
- For the 24-hour delayed dose (double dose), C_{max} was >10% above compliant steady-state levels 2 days after the scheduled administration (Table 1)

Table 1. Percent Increase in C_{max} and C_{min} from Predicted Daily Dosing After a Delayed USL255 Dose

	USL255 6-hr Delay	USL255 12-hr Delay	USL255 18-hr Delay	USL255 24-hr Delay (Double Dose)
One day (24 – 48 hr) after scheduled administration				
C_{max}	4.20	5.96	6.80	7.35
C_{min}	2.83	5.67	10.75	14.86
Two days (48 – 72 hr) after scheduled administration				
C_{max}	2.09	4.25	6.79	11.85
C_{min}	2.55	5.12	7.67	10.23
Three days (72 – 96 hr) after scheduled administration				
C_{max}	1.14	2.95	4.98	7.03
C_{min}	1.33	2.66	3.99	5.31

Abbreviations: C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration.

CONCLUSIONS

- Simulated delayed administration of a single USL255 dose 6, 12, 18, or 24 hours later than scheduled led to incremental decreases in topiramate plasma concentrations prior to the next scheduled dose
- Within 1 day after delayed-dose administration, C_{min} values were at or above the steady-state C_{min} levels with compliant dosing
  - Since C_{min} is commonly associated with efficacy,[9] quickly achieving concentrations above C_{min} is clinically important
- For the 6, 12, and 18 hours delayed-dose scenarios, C_{max} values did not increase >10% above compliant dosing
  - As tolerability may be related to C_{max}, minimizing increases in C_{max} may alleviate unwanted adverse events[10]
- These data demonstrate a fast return to steady-state topiramate plasma concentrations after delayed-dose administration of USL255
- Once-daily USL255, Qudexy™ XR (topiramate) extended-release capsules, has favorable pharmacokinetic properties that may reduce the impact of a delayed dose

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Presented at the 66th Annual Meeting of the American Academy of Neurology
April 26 - May 3, 2014 | Philadelphia, PA

Financial support for this presentation, including writing assistance by Prescott Medical Communications Group (Chicago, IL), was provided by Upsher-Smith Laboratories, Inc.

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