

Uprima™ Clinical Safety and Efficacy

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Presentation Objectives

- To discuss:
 - the efficacy and safety of the 2 mg dose
 - the efficacy and safety of the 4 mg dose
 - the efficacy and safety of the 2 to 4 mg dose titration regimen
 - the efficacy and safety in the diabetic trial
 - the safety results of the 5 and 6 mg doses

Uprima™: Clinical Summary

- | | |
|---|---|
| <p><u>Controlled Phase 3 Trials</u></p> <ul style="list-style-type: none"> ■ Three crossover trials (M96-470, M97-658, M98-941) ■ One parallel-arm trial ■ One diabetic trial ■ One radical prosta- tectomy trial | <p><u>Uncontrolled Phase 3 Trials</u></p> <ul style="list-style-type: none"> ■ Three 6-month extensions (M96-471, M97-659, M98-936) ■ Two 3-year safety studies ■ One dose-titration regimen study |
|---|---|

Uprima™ Efficacy of the 2 mg Dose

- Primary Efficacy Endpoint: Percentage of Successful Attempts

| | Baseline | Placebo | 2 mg |
|---------|----------|---------|------|
| M96-470 | 29 % | 32 % | 46 % |
| M97-658 | 24 % | 38 % | 44 % |
| M98-941 | 29 % | 32 % | 47 % |

Uprima™ Efficacy of the 2 mg Dose

- Secondary Efficacy Endpoint: Percentage of Successful Responders (≥ 50 % successes)

| | Placebo | Uprima™ |
|--------------------------------------|---------|---------|
| All studies combined (n = 388) | 36 % | 48 % |

Uprima™ Safety of the 2 mg Dose

| | Placebo (%) | Uprima™ (%) |
|-------------|-------------|-------------|
| Nausea | 0.8 - 1.4 | 1.6 - 2.6 |
| Dizziness | 2.0 - 3.8 | 2.0 - 4.5 |
| Somnolence | 0.0 - 3.9 | 0.7 - 3.2 |
| Sweating | 0.0 | 0.7 - 2.6 |
| Vomiting | 0.0 | 0.0 - 1.3 |
| Hypotension | 0.0 | 0.0 - 1.2 |
| Syncope | 0.0 | 0.0 - 0.7 |

Uprima™ 2 mg Reports of Syncope and Hypotension

| | Number of reports |
|------------------|-------------------|
| Syncope | 2 |
| Hypotension | 5 |
| Combined | 7 |
| Total dosed | 964 |
| Percent of total | 0.7% |

Uprima™ 2 mg Reports of Syncope

- 68 y/o experienced nausea and syncope after taking two doses of 2 mg within 4 hours. *He was unconscious for "approximately 4 minutes"*.
- 69 y/o experienced nausea, diaphoresis, vomiting and syncope after an in-office dose of 2 mg. *The syncopal event lasted "approximately 3 minutes"*. He received oxygen and Compazine.

Uprima™ 2 mg Reports of Hypotension

- 50 y/o experienced hypotension, *bradycardia*, and sweating approximately 40 minutes after his first 2 mg dose
 - hypotension and bradycardia lasted for 5 and 10 minutes, respectively

Percentage of Patients Remaining on Uprima™ 2 mg Dose

| | 2 mg | 4 mg | 5 mg | 6 mg |
|---------|------|------|------|------|
| M96-471 | 11 % | 27 % | N/A | 62 % |
| M97-659 | 6 % | 29 % | 24 % | 41 % |
| M98-876 | 6 % | 15 % | 79 % | N/A |

Uprima™ Efficacy of the 4 mg Dose

- Primary Efficacy Endpoint: Percentage of Successful Attempts

| | Baseline | Placebo | 4 mg |
|---------|----------|---------|------|
| M96-470 | 27 % | 35 % | 52 % |
| M97-658 | 28 % | 35 % | 56 % |
| M98-941 | 26 % | 31 % | 54 % |

Uprima™ Efficacy of the 4 mg Dose

- Secondary Efficacy Endpoint: Percentage of Successful Responders (≥ 50 % successes)

| | Placebo | Uprima™ |
|-----------------------------------|---------|---------|
| All studies combined (n = 362) | 35 % | 59 % |

Uprima™
Safety of the 4 mg Dose

| | Placebo (%) | Uprima™ (%) |
|-------------|-------------|-------------|
| Nausea | 1.3 - 2.8 | 18.1 - 22.2 |
| Dizziness | 1.4 - 2.6 | 13.4 - 14.5 |
| Somnolence | 0.0 - 1.7 | 8.7 - 12.8 |
| Sweating | 0.0 | 9.4 - 10.3 |
| Vomiting | 0.0 | 1.3 - 4.3 |
| Hypotension | 0.0 | 3.1 - 6.0 |
| Syncope | 0.0 | 0.9 - 2.0 |

Uprima™ 4 mg
Reports of Syncope and Hypotension

| | Number of reports |
|------------------|-------------------|
| Syncope | 11 |
| Hypotension | 31 |
| Combined | 42 |
| Total dosed | 1279 |
| Percent of total | 3.3% |

Uprima™ 4 mg
Reports of Syncope

- 33 y/o received 4 mg and was observed for 30 minutes in-office; while driving home, he experienced nausea, fatigue, flushing and sweating. He attempted to stop his car, but he *lost consciousness and crashed into a fence.*
- 36 y/o experienced pallor, diaphoresis and syncope approximately 30 minutes after his first in-office dose of 4 mg. He *lost consciousness for 3 seconds.* He was *tired, weak and flushed for 8 hours* after the episode.

Uprima™ 4 mg
Reports of Syncope

- 50 y/o experienced nausea after first in-office dose of 4 mg and requested Compazine. He had previously tolerated 2 mg without incident. Upon returning with the medication, the nurse found him *unconscious, apneic, unresponsive, diaphoretic and incontinent of urine.* Within a few seconds, he awoke and began to breathe. His HR was 42 bpm. He received IV saline, oxygen and Compazine. He was *admitted to the hospital due to persistent bradycardia (> 1 hour).*

Uprima™ 4 mg
Reports of Syncope

- 60 y/o experienced syncope 35 minutes after his first dose of 4 mg. He was unconscious for 3 seconds. His "head was adjusted, rousing (him)". He was *pale, hot, diaphoretic and vomiting.* He was moved to a supine position and his symptoms improved over an hour.

Uprima™ 4 mg
Reports of Syncope

- 69 y/o complained of diaphoresis 38 minutes after his first dose of 4 mg. His blood pressure at that time was 117/50 mm Hg and heart rate was 60 bpm. He then fainted and was *unresponsive for 2 minutes.* He was given oxygen and intravenous fluids.

Uprima™ 4 mg Reports of Hypotension

- 60 y/o experienced hypotension (BP 70/41 mm Hg), bradycardia (HR 45 bpm), pallor, fatigue, and sweating 35 minutes after his first in-office dose of 4 mg. He did not lose consciousness. He was placed supine and given water to drink. The symptoms abated within 2 hours of dosing.

Uprima™ 4 mg Reports of Hypotension

- 56 y/o received 4 mg in-office despite complaining of diarrhea and abdominal cramps earlier in the day. After the dose, he experienced severe hypotension. He was unconscious for "15 to 20 minutes". Upon awakening, he vomited. He was transported to ER, where he lost consciousness again. BP was 60 mm Hg palpable. EKG revealed ST-T changes. He received IV fluids in ICU.

Uprima™ 4 mg Reports of Hypotension

- 59 y/o experienced moderate hypotension, dizziness, nausea and sweating approximately 25 minutes after his first in-office dose of 4 mg. His BP was 72/50 mm Hg. The duration of the hypotension was 105 minutes.

Uprima™ Efficacy of the 2 → 4 mg Dose

- Primary Efficacy Endpoint: Percentage of Successful Attempts

| | n | Mean |
|----------|-----|------|
| Placebo | 119 | 35 % |
| 2 → 4 mg | * | 48 % |
| 2 → 6 mg | 242 | 54 % |
| 5 mg | 89 | 55 % |
| 6 mg | 119 | 53 % |

Uprima™ Dose Titration Study Adverse Events

| | Hypotension or Syncope |
|----------|------------------------|
| Placebo | 0.8 % |
| 2 → 6 mg | 5.4 % |
| 5 mg | 5.0 % |
| 6 mg | 3.4 % |

Uprima™ Efficacy in the Diabetic Study

- Primary Efficacy Endpoint: Percentage of Successful Attempts

| | Placebo | Uprima™ |
|------------------|---------|---------|
| 4 mg (n = 90) | 15 % | 25 % |

Uprima™ Efficacy in the Diabetic Study

■ Secondary Efficacy Endpoint: Percentage of Successful Responders (≥ 50 % successes)

| | Placebo | Uprima™ |
|------------------|---------|---------|
| 4 mg (n = 90) | 16 % | 25 % |

Uprima™ Diabetic Study Adverse Events

| | Hypotension or Syncope |
|---------|------------------------|
| Placebo | 1.0 % |
| 4 mg | 4.0 % |
| Placebo | 0.0 % |
| 5 mg | 3.8 % |

Uprima™ Safety of the 5 and 6 mg Doses

| | Placebo (%) | 5 mg (%) | 6 mg (%) |
|-------------|-------------|-------------|-------------|
| Nausea | 1.5 - 2.5 | 29.2 - 32.8 | 35.3 - 42.5 |
| Dizziness | 0.0 - 3.4 | 20.1 - 20.3 | 16.4 - 22.6 |
| Sweating | 0.0 - 0.9 | 14.8 - 16.9 | 19.6 - 20.7 |
| Somnolence | 0.0 - 1.7 | 11.7 | 11.6 - 17.2 |
| Vomiting | 0.0 | 7.1 - 10.2 | 8.6 - 13.0 |
| Hypotension | 0.0 | 2.3 - 6.5 | 4.3 - 4.8 |
| Syncope | 0.0 | 2.6 - 3.5 | 2.1 - 2.3 |

Uprima™ A Safety Risk?

■ A 42 y/o received a 5 mg in-office dose. He had tolerated 2 mg and 4 mg. One hour after dosing, he felt nauseated and stood up to "find someone." The nurse found him *unconscious, bleeding from a tongue laceration and from a head abrasion*. After smelling salts, he awoke. Within 15 minutes he felt better.

Five days later he complained of a headache. CT scan revealed a *left occipital skull fracture* with a cortical contusion. MRI showed a *non-depressed skull fracture* and a *contra-coup injury of the right frontal lobe*.

Uprima™ A Safety Risk?

■ A 63 y/o received a 5 mg in-office dose. He had previously tolerated 2 mg and 4 mg. Shortly after dosing, he felt nauseated, light-headed and clammy. He recalls going to the door "for assistance". He was found, *bleeding from a head laceration*. It was assumed he hit his head on a nearby table.

Nausea lasted for 50 minutes and light-headedness for 80 minutes

Percentage of Patients Discontinuing Therapy

| | Study Duration | Reason for Discontinuation | | | |
|---------|----------------|----------------------------|------------------|-----------------|---------------|
| | | Total Disc. | Lack of Efficacy | Patient Request | Adverse Event |
| M96-471 | 6 mos. | 63 % | 29 % | 16 % | 10 % |
| M97-659 | 6 mos. | 59 % | 33 % | 11 % | 16 % |
| M97-682 | 3 yrs. | 60 % | 32 % | 17 % | 10 % |
| M97-793 | 3 yrs. | 59 % | 34 % | 9 % | 10 % |

Uprima™ 2 mg Summary Comments

- Modest benefit compared to placebo
 - responder rate 36% for placebo vs. 48% for Uprima™
- Overall incidence rate of syncope/hypotension adverse event reports of 0.7%
- Few patients (6 to 11%) choose to remain on the 2 mg dose

Uprima™ 4 mg Summary Safety Comments

- Overall incidence rate of syncope and hypotensive adverse event reports of 3.3% (about 1 in 30 patients)
- Evidence of:
 - persistent bradycardia
 - prolonged hypotension
 - serious injury (skull fracture, car crash, head laceration)
 - urgent medical intervention to prevent serious injury (IV fluids, oxygen, atropine, hospitalization)

Uprima™ 4 mg Summary Safety Comments

- Syncope and hypotensive events
 - usually occurred in a doctor's office
 - generally, but not always, limited to the first dose or to the first increase in dose
 - occurred despite careful dose titration

Uprima™ 2→4 mg Summary Comments

- 2→4 mg
 - Mean percentage of successful attempts
 - Placebo 35%
 - Uprima™ 48%
- Adverse events
 - Syncope/hypotension rate highest in the dose- titration arm:
 - dose-titration 5.4 %
 - 5 mg fixed dose 5.0 %
 - 6 mg fixed dose 3.4 %
 - placebo 0.8 %

Uprima™ Diabetic Study Summary Comments

- Efficacy
 - mean percentage of successful attempts (4 mg)
 - Placebo 15%
 - Uprima™ 25%
- Safety
 - incidence of hypotension and syncope
 - Placebo 1.0%
 - Uprima™ 4.0%

Uprima™ 5 and 6 mg Summary Safety Comments

- Incidence of nausea, dizziness, sweating, somnolence and vomiting are greater
- Doses discontinued by the sponsor during Phase 3
- Higher incidence of adverse events:
 - hypotension 2.3 - 6.5 %
 - syncope 2.1 - 3.5%
- Pharmacologically, little difference between 4 mg, 5 mg and 6 mg