

Avanafil: Investigational Drug for ED



Introduction

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Summary of avanafil program

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TA-314: Long-term safety and efficacy

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Background

- Erectile dysfunction (ED) affects up to 18 million men in the United States.¹
 - In men with diabetes, the prevalence may be more than 70%.²
- Phosphodiesterase type 5 (PDE5) inhibitors are first-line treatment for ED.
 - Currently available PDE5 inhibitors generally administered 60-120 minutes prior to sexual activity.^{3,4}
- Avanafil is an investigational PDE5 inhibitor
 - Rapidly absorbed
 - Highly specific for PDE5 isoenzyme
 - Short half-life

1. Selvin E, et al. *Am J Med* 2007;120(20):151-157. 2. Giuliano FA. *Urology* 2004;64(6):1196-1201.

3. Corbin JD. *Int J Impot Res.*2004;16(suppl 1):S4-S7. 4. Rosen RC, Kostis B. *Am J Cardiol* 2003;92(9A):9M-18M.

Avanafil Phase 3 Program

Studies	Population	Total Enrolled	Duration	Status
REVIVE (TA-301)	General	646	16 wks	Completed
REVIVE-D (TA-302)	Diabetics	390	16 wks	Completed
REVIVE-S (TA-314)	Open label	493 153	6 mos 1 year	Completed
REVIVE-RP (TA-303)	Radical Prostatectomy	298	16 wks	Completed Not required for NDA

Standard Study Design

- 4 week run-in, 12 weeks of treatment as needed for sexual activity
- Co-primary endpoints:
 - Sexual Encounter Profile Question 2 (Erection sufficient for penetration)
 - Sexual Encounter Profile Question 3 (Erection sufficient for successful intercourse)
 - International Index of Erectile Function-EF domain

TA-301: General ED

- Results:

	<u>Placebo</u>	<u>200mg</u>
– SEP 2	54%	77%
– SEP 3	27%	57%
– IIEF	15.3	22.2
- All 3 doses of avanafil were effective compared to placebo for all 3 co-primary endpoints ($p \leq 0.001$)
- Successful intercourse (SEP 3) was reported in subjects with attempts at ≤ 15 minutes and > 6 hours
- Avanafil was well tolerated with low rates of typical PDE5-type side effects in this generalized ED population

TA-302: Diabetics

- Results:

	<u>Placebo</u>	<u>200mg</u>
– SEP 2	42%	63%
– SEP 3	20%	40%
– IIEF	13.2	17.3
- Both doses of avanafil were effective compared to placebo for all 3 co-primary endpoints ($p \leq 0.002$)
- Successful intercourse (SEP 3) was reported in subjects with attempts at <15 minutes and >6 hours
- Avanafil was well tolerated with low rates of typical PDE5-type side effects in this diabetic population with ED

TA-303: Radical Prostatectomy Patients

- Randomized, double-blind, placebo-controlled, parallel group, multicenter study of the safety and efficacy of avanafil in the treatment of erectile dysfunction following bilateral, nerve-sparing, radical prostatectomy in 298 men with ED
- On average, subjects entering the study were 58 years old, 19 months past their surgery dates and diagnosed with severe ED
- Study met all primary endpoints including improvements in SEP2, SEP3, IIEF
- Success observed in as early as 15 minutes
- The most common side effects were headache, flushing and nasopharyngitis, and dropouts due to adverse events were low. There were no serious adverse events reported in the study.
- Detailed results of the study will be presented during the upcoming Cancer Survivorship Symposium to be held during the International Society of Sexual Medicine meeting in Washington DC
- The results of the RP study are not required for the avanafil NDA, but the final study report will be submitted to the FDA upon completion

An Open-Label, Long-term Evaluation of the Safety and Efficacy of Avanafil in Men With Erectile Dysfunction

Laurence H. Belkoff, DO

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TA-314 Study Design: Open-Label Extension Study

- Long-term safety, efficacy, and tolerability of avanafil in men (N=712) with or without diabetes and mild-to-severe ED.
 - **TA-314:** up to 52-week, open-label extension study of two 12-week studies
 - **TA-301:** double-blind, placebo-controlled, Phase 3 trial of men with mild-to-severe ED.
 - **TA-302:** double-blind, placebo-controlled, Phase 3 trial of men with mild-to-severe ED and type 1 or type 2 diabetes.
 - Preplanned extension study: enrollment was halted once the required number of subjects enrolled into the extension study.
 - Per FDA requirements, 300 subjects were planned through 26 weeks and 100 subjects through 52 weeks.
 - Subjects were started on 100 mg and were instructed to take 1 dose of study drug 30 minutes prior to initiation of sexual activity.
 - Subjects were permitted to increase dose to 200 mg to increase efficacy and were permitted to decrease dose to 50 mg to improve tolerability.

TA-314 Baseline Demographics (Enrolled Subjects)

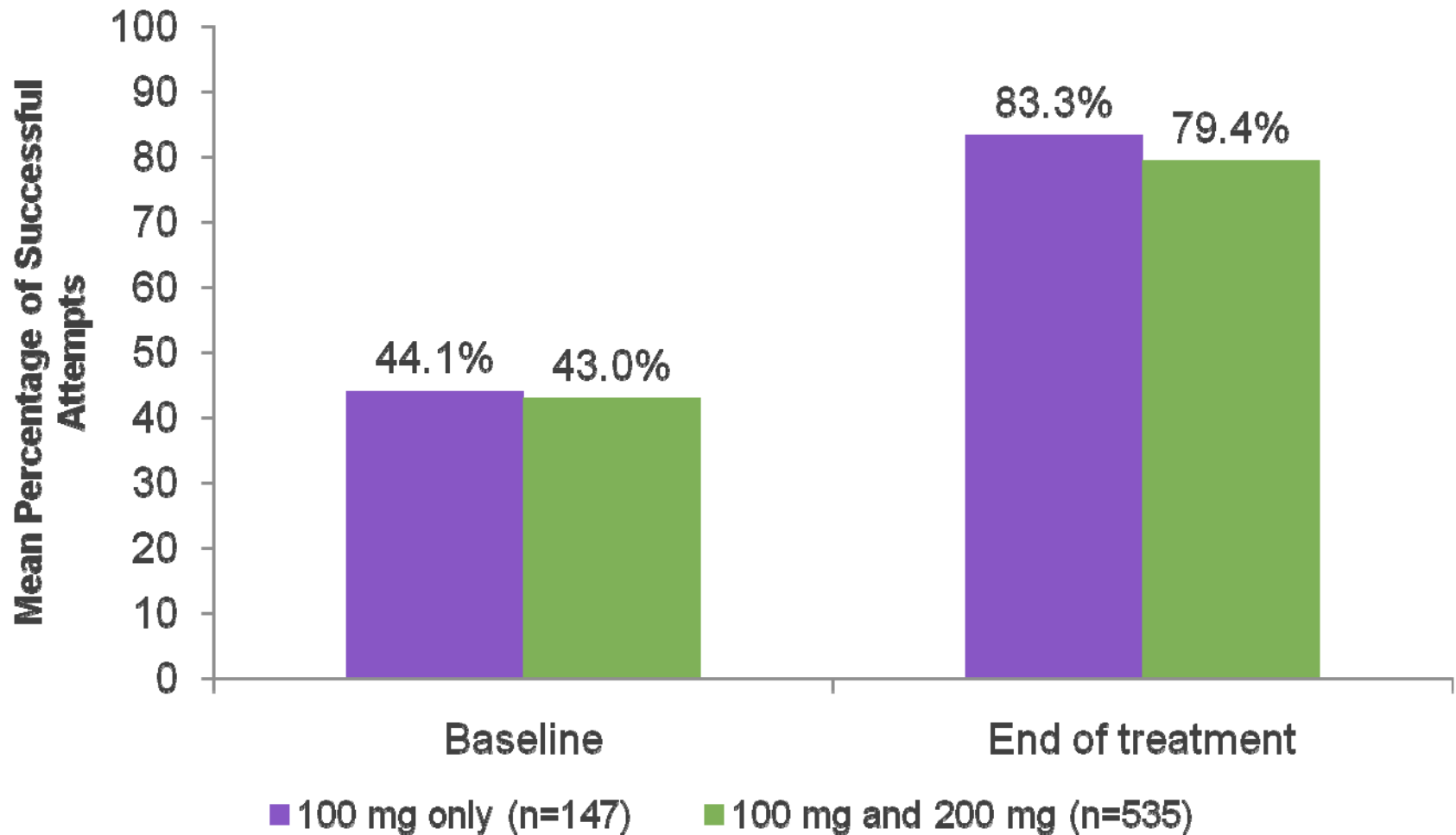
	100 mg only (n=171)	100 mg and 200 mg*† (n=536)	Total‡ (N=712)
Mean age, years (SD)	54.2 (10.9)	57.1 (9.9)	56.4 (10.2)
Caucasian, n (%)	147 (86.0)	459 (85.6)	610 (85.7)
ED severity, n (%)			
Mild	64 (37.4)	142 (26.5)	207 (29.1)
Moderate	59 (34.5)	177 (33.0)	238 (33.4)
Severe	48 (28.1)	217 (40.5)	267 (37.5)
Mean ED duration, months (SD)	63.7 (58.6)	79.8 (72.3)	75.9 (69.4)
History of diabetes, n (%)	63 (36.8)	162 (30.2)	226 (31.7)
Type 1	6 (3.5)	14 (2.6)	20 (2.8)
Type 2	57 (33.3)	148 (27.6)	206 (28.9)

*Subjects who were dosed with both avanafil 100 mg and 200 mg over the course of the study.

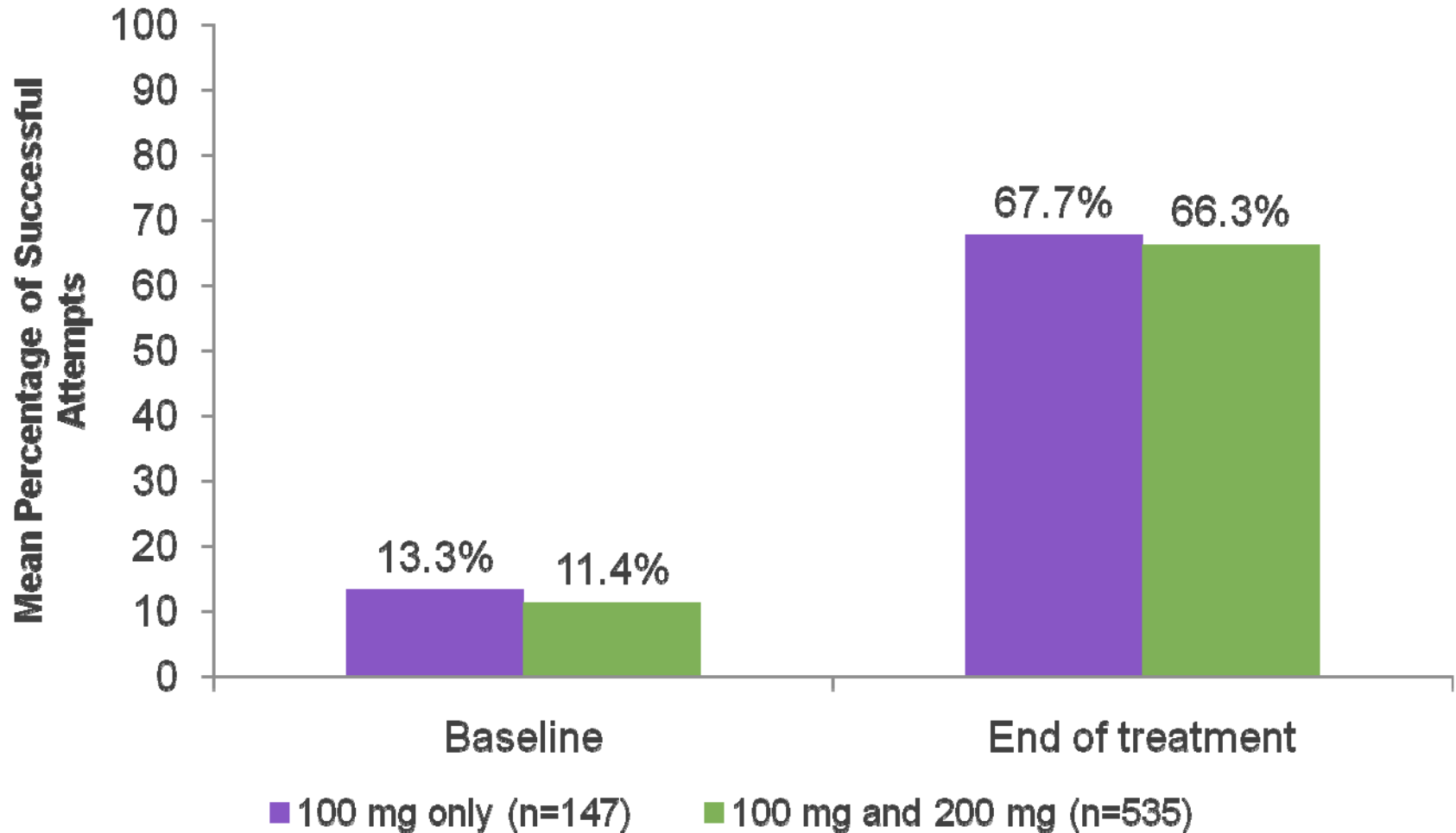
†Subjects who tolerated 100 mg were permitted to increase dose to 200 mg, and subjects who were unable to tolerate 100 mg were permitted to decrease dose to 50 mg.

‡3 subjects received avanafil 100 mg and 50 mg, 1 subject received all 3 doses of avanafil, and 1 subject did not receive study drug during this extension study.

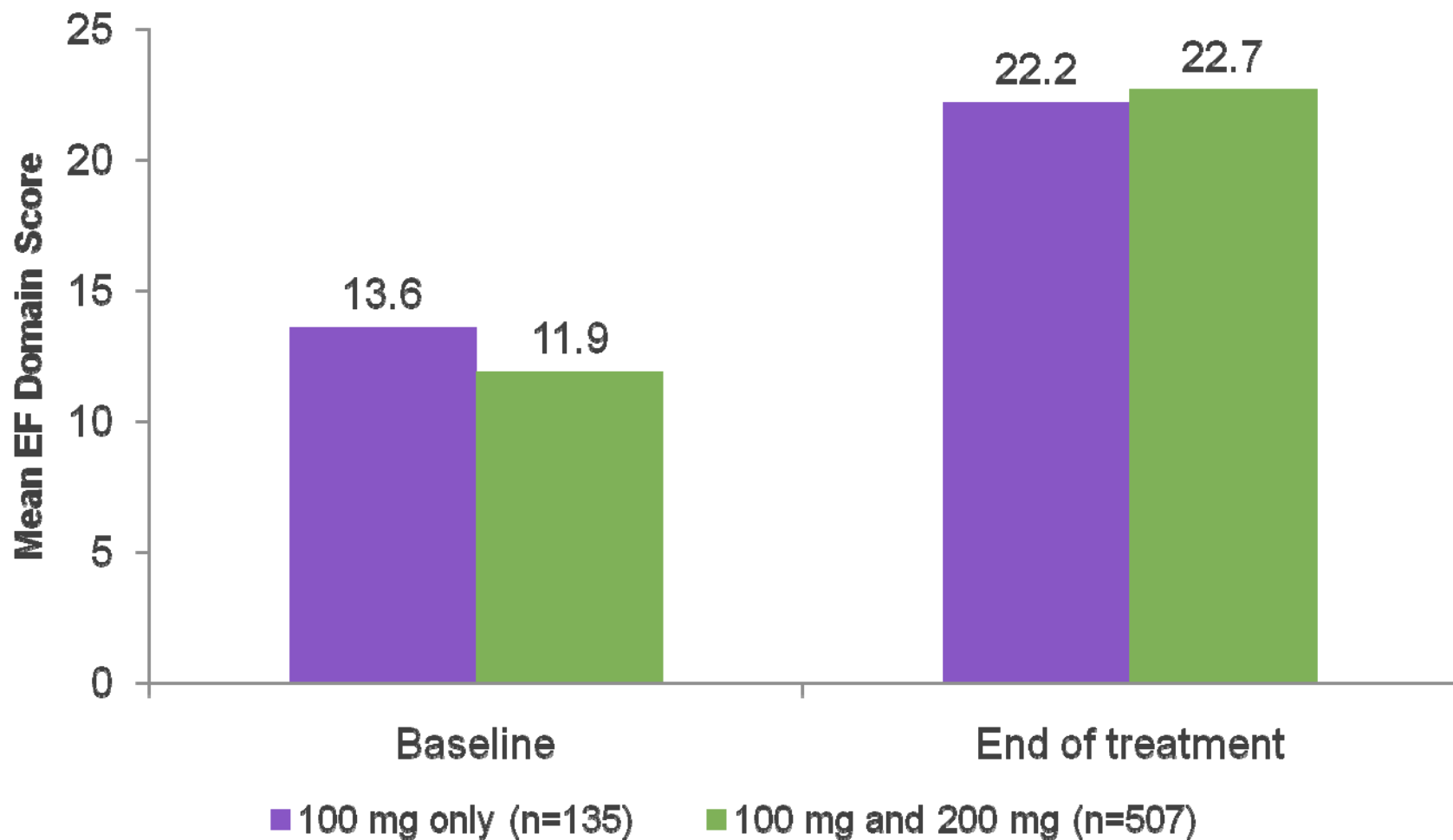
TA-314 Percentage of Successful Penetration Attempts (SEP 2; ITT)



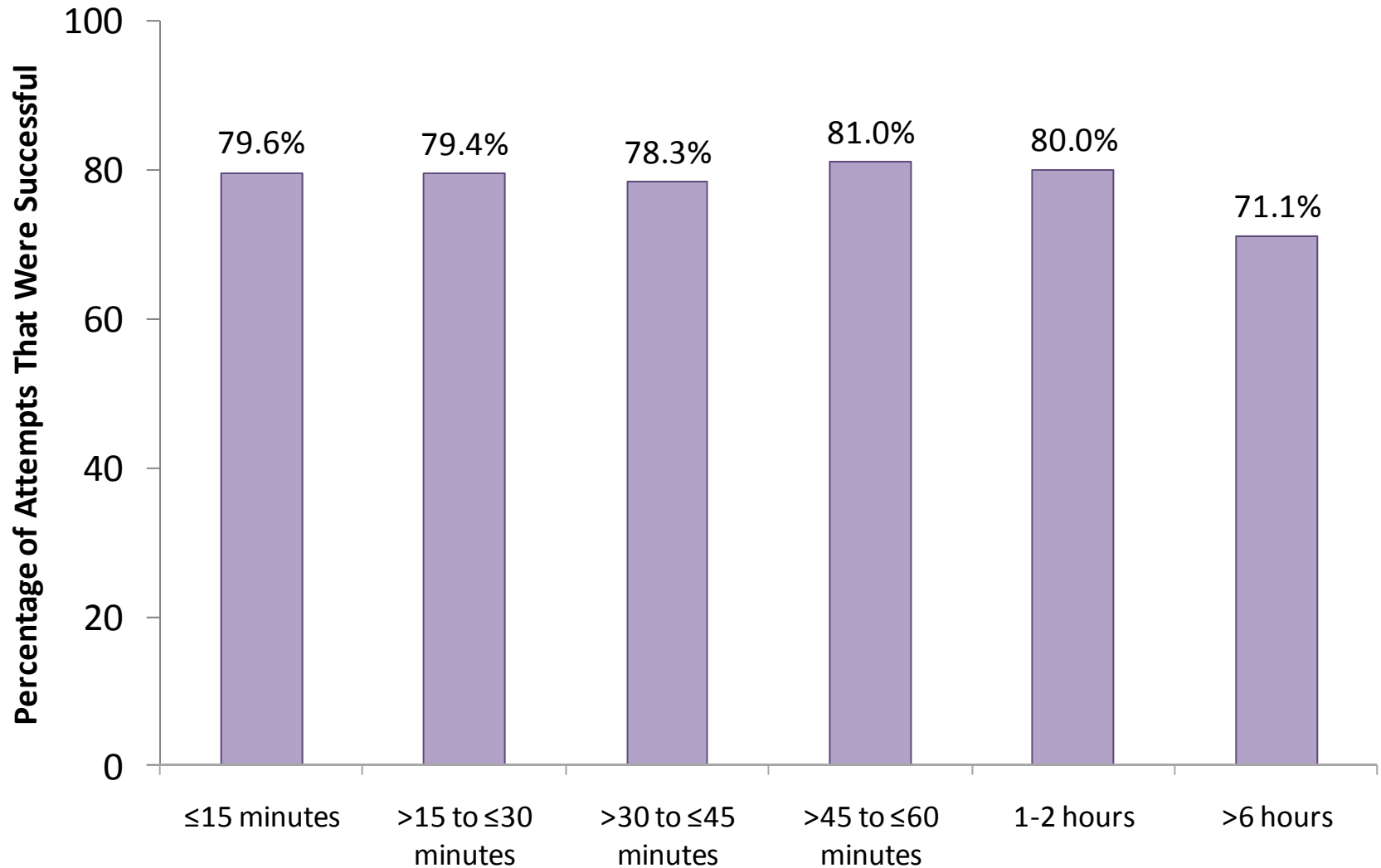
TA-314 Percentage of Successful Intercourse Attempts (SEP 3; ITT)



TA-314 IIEF-EF Domain Score (ITT)



Successful Intercourse by Time Interval From Dose to Attempt (SEP 3; ITT)*



*Represents total sexual attempts by the ITT population (n=686).

TA-314 Most Common Treatment-Emergent Adverse Events (Safety Population)

Subjects with any TEAE, n (%)	Total (N=711)
Headache	40 (5.6)
Nasopharyngitis	24 (3.4)
Flushing	25 (3.5)
Nasal congestion	15 (2.1)
Influenza	11 (1.5)
Back pain	11 (1.5)

TEAE=treatment-emergent adverse event.

TA-314 Summary

- Data suggests that avanafil was an effective, long-term treatment for ED, with improvements observed for up to 1 year.
- Avanafil was effective as rapidly as 15 minutes and, in some subjects, beyond 6 hours after dosing.
 - Across the study, 84% of all sexual attempts were made within 60 minutes of dosing.
- Avanafil was generally well tolerated over 52 weeks, with a low dropout rate due to AEs (<3%).
- Avanafil may represent a PDE5 inhibitor with a fast onset and good tolerability.

Erectile Dysfunction (ED) Market Opportunity

- Erectile dysfunction afflicts up to 30M men in the US¹,
- In 2010, PDE5 inhibitors generated revenues of \$4.1B²
 - Sildenafil \$1.9B
 - Tadalafil \$1.7B
 - Vardenafil \$0.5B
- 50% of patients using PDE5 inhibitors are unsatisfied¹, creating opportunities for new entries
- Physicians switch many patients to another PDE5 inhibitor due to lack of efficacy and/or side effects³

¹ Global Industry Analysts, Inc. – Erectile Dysfunction Drugs: A Global Market Report, April 2010

² Annual reports

³ Primary market research May 2010 – Life Sciences Strategies Group

Summary: Avanafil for Erectile Dysfunction

- Significant efficacy seen in all phase 3 studies
 - 80% success rate in SEP2 (penetration)
 - 67% success rate in SEP3 (persistence)
 - Patients attempting SEP3 as early as 15 minutes after dosing were successful
- Highly selective PDE5 inhibitor
 - Most common side effects were headache, flushing, common cold, nasal congestion
- Efficacy was independent of food or alcohol
- NDA to be filed Q2 2011