국내신약(자이데나정)의 개발경험

Udenafil (Zydena®)

A Novel PDE5 Inhibitor

- 개발경위
  Developmental History
  Preclinical data
  Clinical data

- 고려사항

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Dong-A Pharm

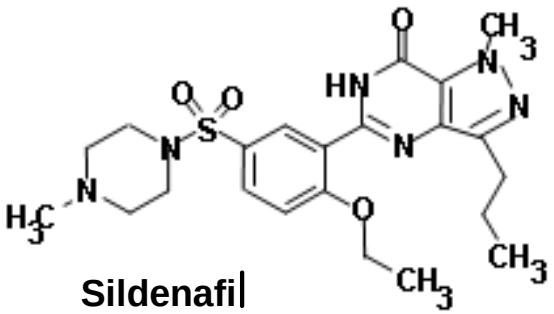
Udenafil

- Zydena® (udenafil) – Unique Selling Proposition
  - Zydena® is the 4th PDE5i in ED market
  - Zydena® is DIFFERENT, first 24 hour product
    - A faster, more efficacious, long acting product – a better Cialis
  - Zydena® has LESS SIDE EFFECTS (myalgia, back pain, dyspepsia)
    - Lower side effects appeals to many patients

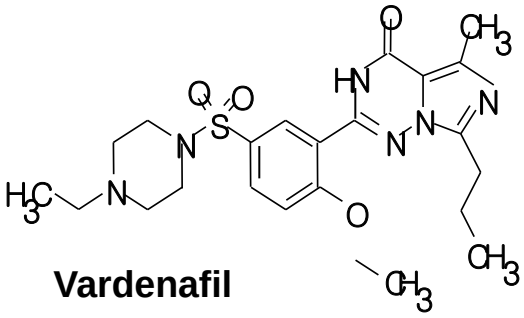
- Korean market adoption of 21% volume share in 2006
  - Zydena® successfully launched in Korea and garner #2 in the ED market

- Becoming a Global Product
  - Launched in Russia Approved in Uzbekistan, Philippines, Turkey, Malaysia..
  - P3 pivotal studies in the US were finished (2011. 2Q NDA)

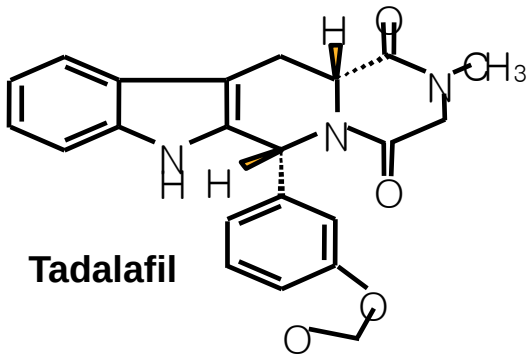
Structure of PDE5Is



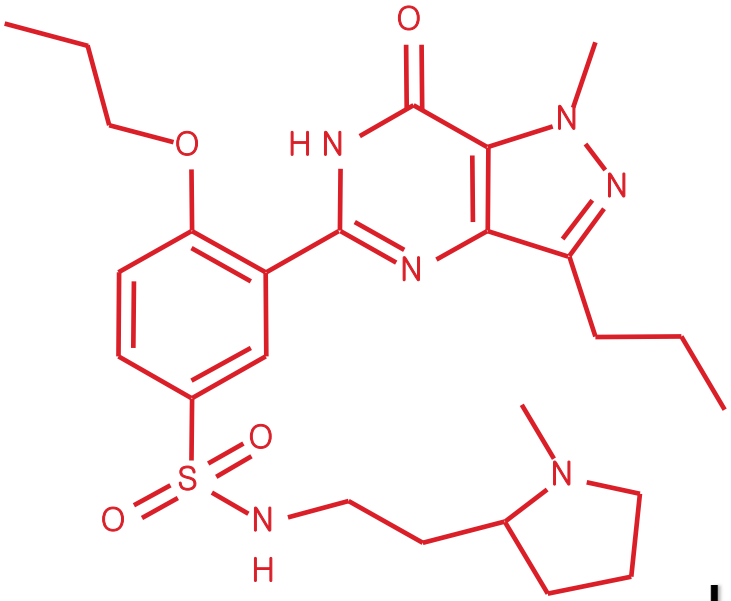
Sildenafil



Vardenafil



Tadalafil



Udenafil


Sildenafil Vardenafil Tadalafil Udenafil Mirodenafil Avanafil

History of Zydena

Time	Events
Jan. 1997	Development
Jan. 1999	Pre-clinical study
Nov. 1999	Patent application
May 2001	Phase I clinical study in Korea
April 2002	Phase I clinical study in Europe (U.K.)
May 2003	Phase II clinical study in Korea
Sep. 2004	Phase III clinical study in Korea
May 2005	Phase II clinical study in USA
Dec. 2005	Approval in Korea
Jun. 2006	Phae IV for DM/HTN
Aug. 2008	Approval in Russia

Pharmacokinetic Characteristics

	Udenafil (Zydena)	Sildenafil (Viagra)	Tadalafil (Cialis)	Vardenafil (Levitra)
Tablets	100, 200 mg	25, 50, 100 mg	10, 20 mg	5, 10, 20 mg
Half-life	11 – 13 hrs	4 hrs	17.5 hrs	4 hrs
Onset	30– 40 mins	30-60 mins	45 mins (?)	30-60 mins
Duration	24 hrs (est.)	4 - 8 hrs	36 hrs	6 - 8 hrs
Selectivity to PDE6	X10	X10	X190	X10
Selectivity to PDE11	> X3000	X780	X5	X1160
Major ADE	Headache Facial flushing	Headache Facial flushing Blue-tinged vision	Headache Indigestion Myalgia	Headache Upset stomach

Preclinical Data Of Zydena

❖ Physicochemical Properties

✓ Favorable solubility in GIT pH range

Solubility (μg/ml)

	pH 2	pH 5	pH 7
Udenafil	44,560	34,420	758
Sildenafil citrate	60,000	8,200	72
Sildenafil	1,600	480	9

✓ Chemically Stable for 36 months

❖ Metabolization

- ✓ **Metabolic stability**

  Udenafil > Sildenafil **in human, rat, and dog liver microsomes**

- ✓ **Pathway**

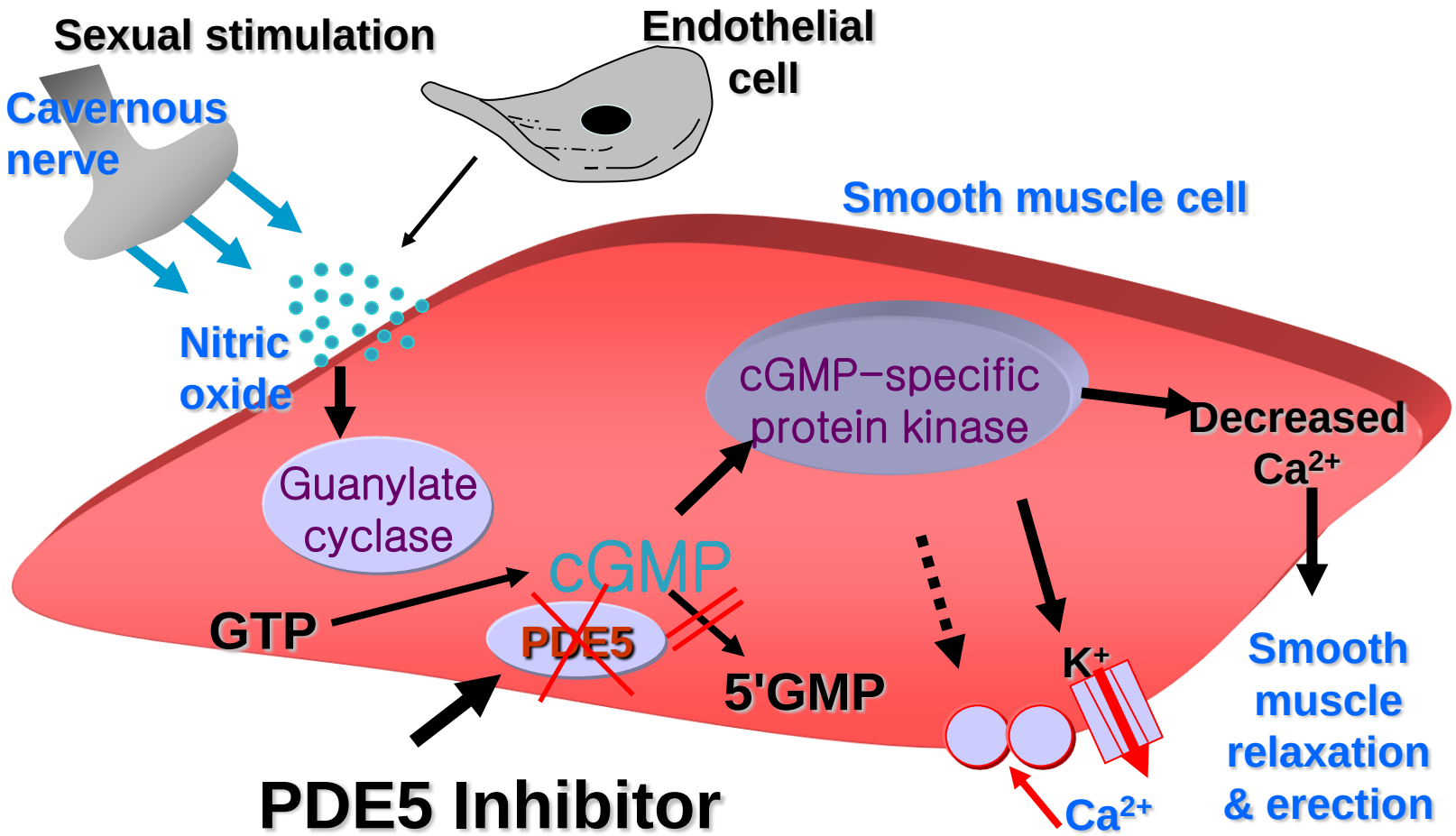
  CYP 3A4

- ✓ **No induction or inhibition of CYP isozymes**

- ✓ **Protein Binding (human plasma)**

Udenafil	**94%**
Sildenafil	**95%**

PDE5I: MODE OF ACTION



Types of PDEs

PDE	Substrate Specificity	Main tissue localization
1	cGMP > cAMP	Brain, heart, vascular smooth muscle
2	cGMP = cAMP	Adrenal cortex, brain, corpus cavernosum (CC)
3	cAMP	Heart, CC, liver, vascular smooth muscle
4	cAMP	Lung, mast cells, vascular smooth muscle, CC
5	cGMP	CC, vascular smooth muscle, platelets, GI tract
6	cGMP > cAMP	Retina
7	cAMP >> cGMP	Skeletal muscle, T cells
8	cAMP	Testes, thyroid
9	cGMP	Broadly expressed, not well characterized
10	cGMP > cAMP	Brain, testes
11	cAMP = cGMP	Testes, heart, skeletal muscle, prostate, liver, kidney, pituitary

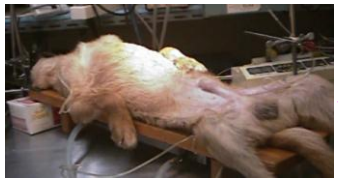
Source: E. Bischoff, IJIR (2004) 16:S11-S14

Isozyme Fold Selectivity vs PDE-5 (IC_{50} of udenfil for PDE5 is 5nM)

Isozyme	Long Acting		Short Acting	
	Udenafil (Zydena)	Tadalafil (Cialis)	Sildenafil (Viagra)	Vardenafil (Levitra)
PDE-1	1,262	>4,450	80	500
PDE-2	560	>14,800	>8,570	44,290
PDE-3	4,460	>14,800	4,630	>7,140
PDE-4	512	>14,800	2,190	43,570
PDE-5	5	6.74	3.5	0.14
PDE-6 (rod)	60	187	11	25
PDE-6 (cone)	400	193	10	4
PDE-7	980	>14,800	6100	>214,000
PDE-8	>2,000	>14,800	8500	>214,000
PDE-9	>2,000	>14,800	750	4,150
PDE-10	686	>14,800	2800	21,200
PDE-11	96	5	780	1,160

Efficacy by Dog ICP Measurement

Animals : experimental dogs
Administration : single i.v. (1-300 μg/kg)
Erectogen : SNP(10 μg/head) was injected into c.c. 4 min after drug administration.
Monitoring : ICP, BP, HR

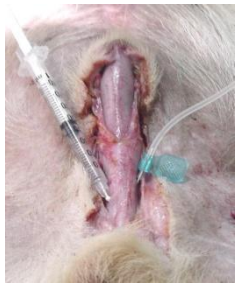


Systemic anesthesia

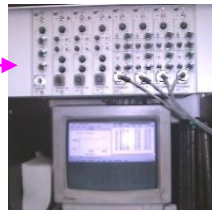
BP/HR monitor. (femoral a.)

Udenafil i.v. (cephalic v.)
4 min

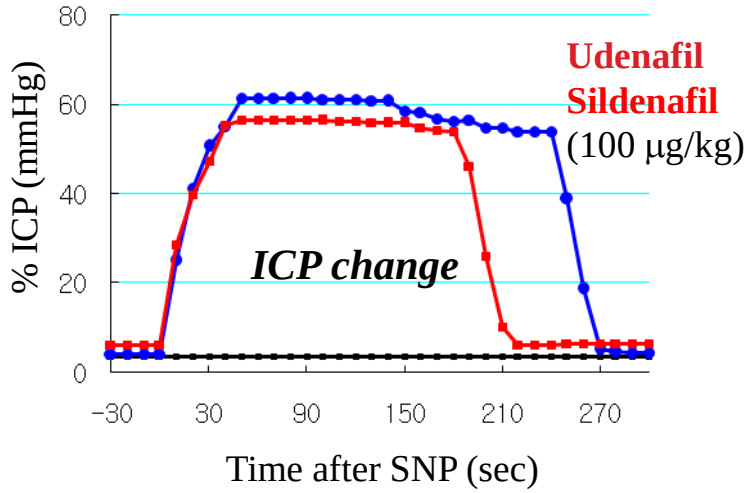
SNP i.c.

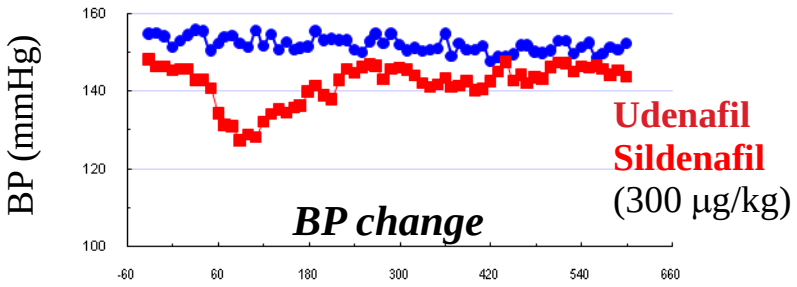


ICP



Signal processing

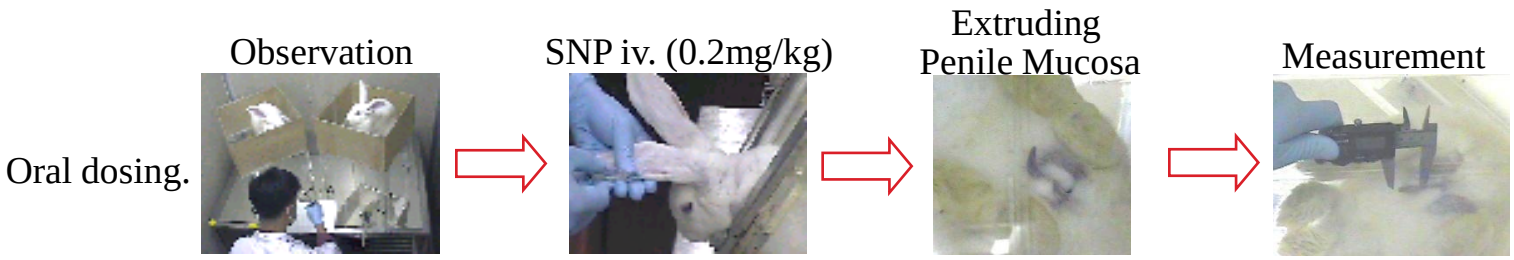


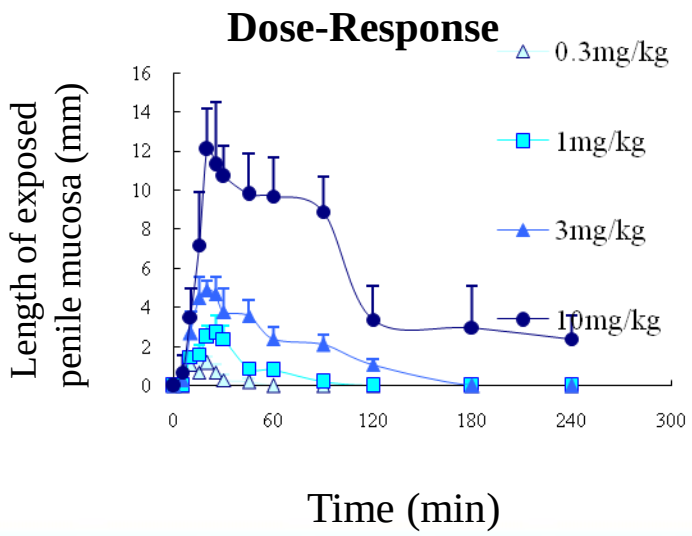


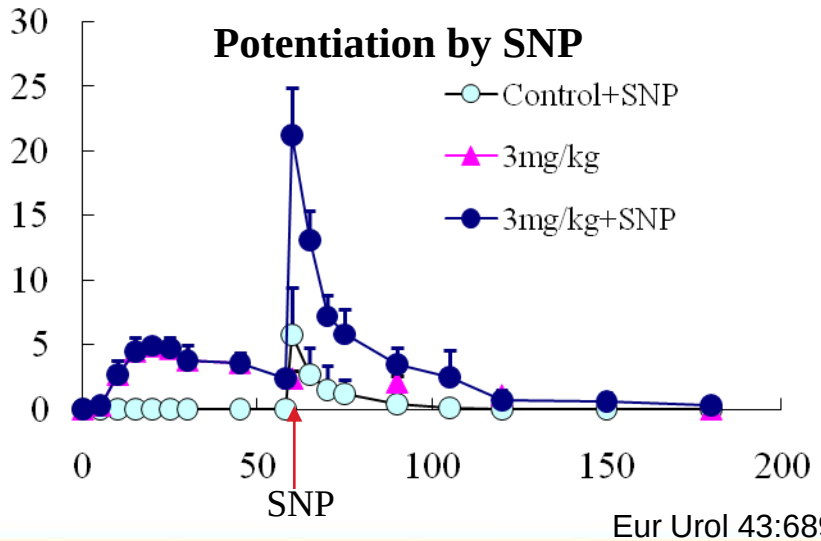
Arch Pharm Res 23:471, 2000

Oral efficacy in conscious rabbits

-Male albino rabbits (3.5-4 kg)
-Oral administration of Udenafil or sildenafil (0.3 ~ 10 mg/kg), following SNP (0.2mg/kg, iv)
-Measuring uncovered penile mucosa up to 4 hrs after drug treatment







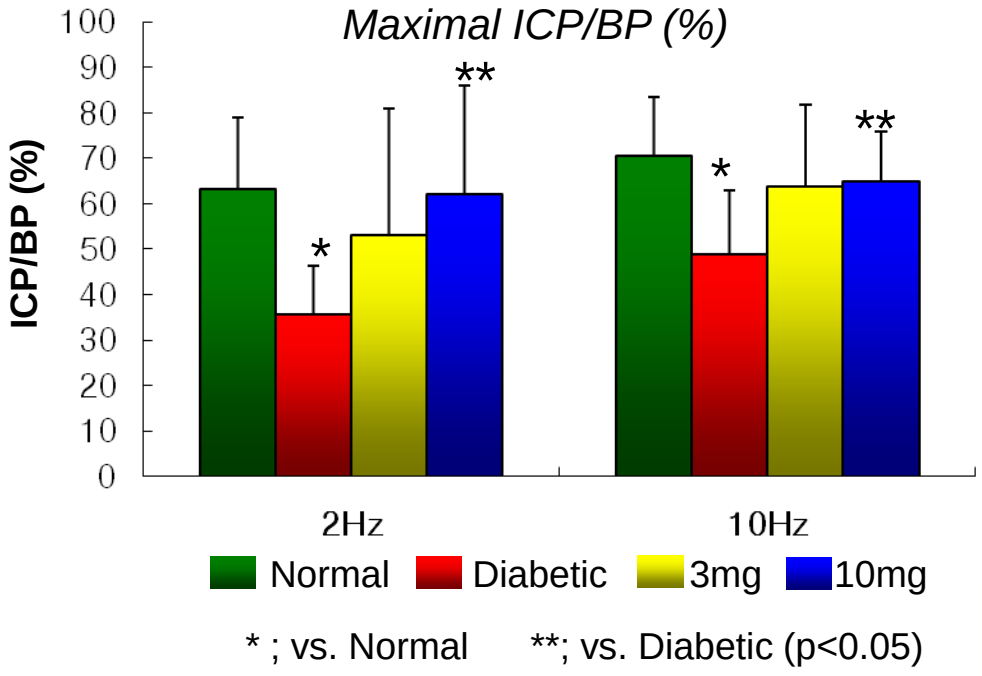
Eur Urol 43:689, 2003

Efficacy in diabetic rat model

Induction of DM: streptozotocin (55mg/kg. i.v.)
Intracavernous pressure : 8 weeks after DM induction, Udenafil (3, 10mg/kg oral), 1 hour before ICP measurement (2, 10Hz, 5msec, 3V, 60sec)

ICP at Lt. CC

BP at carotid a.

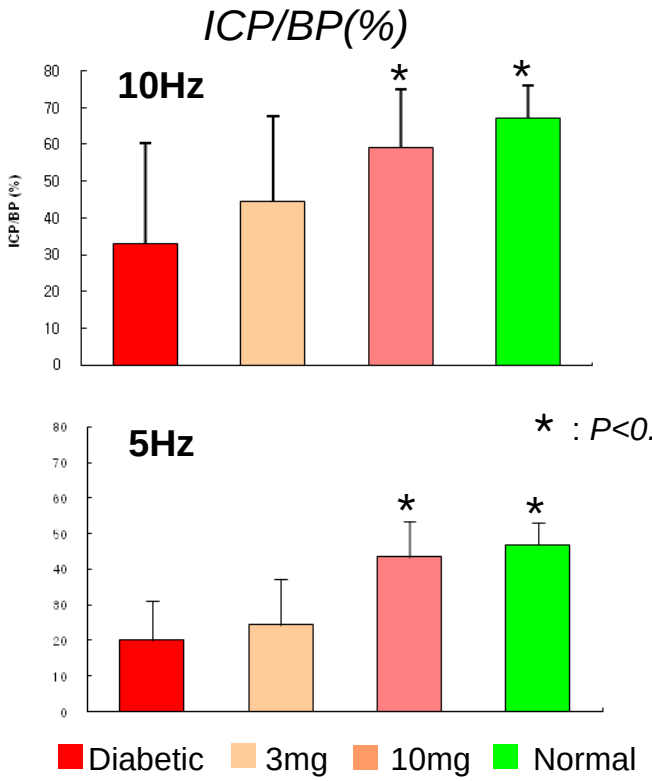


* ; vs. Normal **; vs. Diabetic ($p<0.05$)

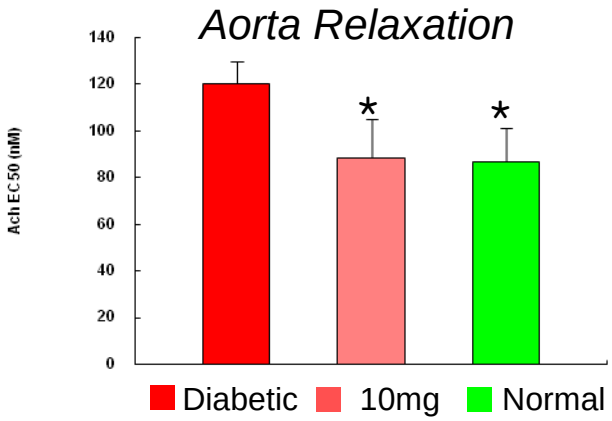
Urol Res 32:107, 2004

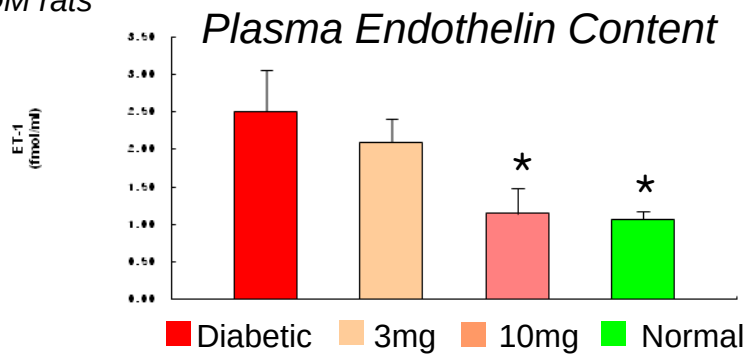
Preservation of erectile function in DM rats

Treatment : Udenafil (3, 10mg/kg, orally) once a day for 8 weeks to STZ induced-DM rats
Measurement: ICP/BP, thoracic aorta relaxation, plasma endothelin level



* : *P<0.05 vs. DM rats*





Int J Impot Res 17:134, 2003

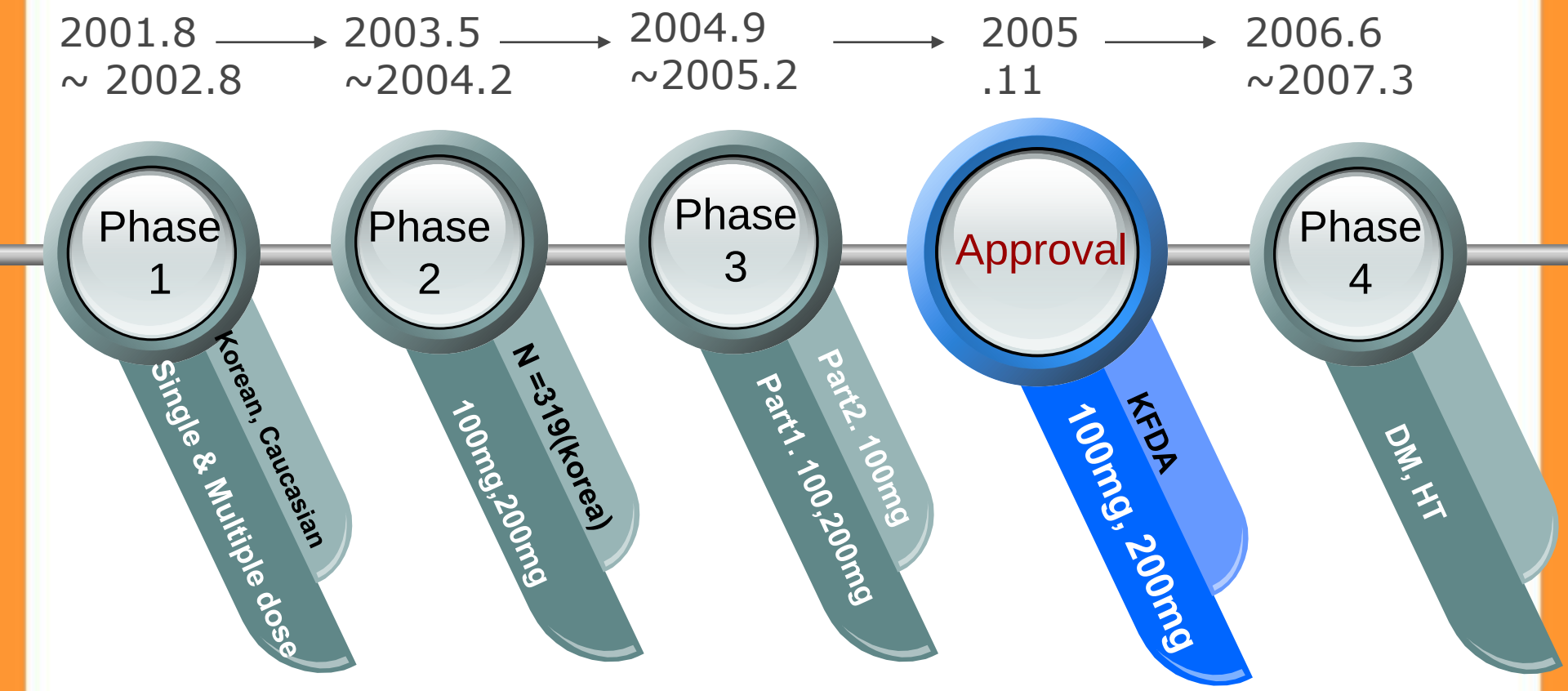
Summary of Toxicity

- **Comparable Short-term toxicity pattern to sildenafil**
- **No Genotoxicity**
- **No Chronic toxicity up to 50 mg/kg (High safety margins)**
- **No QT prolongation issues at therapeutic range**
- **No sperm toxicity up to MTD in rats and dogs**
- **No carcinogenicity in rats and mice**

Biopharm Drug Dispos 2001, 22(3):109

Results of Clinical Study

Clinical Study - *process*



Summary of Phase 1

- Both single dose escalation study (P1a) and multiple ascending dose study (P1b) were conducted in Korea and in U.K.
- Udenafil was **well-tolerated**. No severe or serious adverse events found. Frequently occurring events include " Headache, Erection, Facial flushing"
- PK analysis disclosed "Udenafil has **Tmax of 1 hour post-dosing and $T_{1/2}$ of 11 – 13 hours**"

Zydena® Phase 1
-Interaction Study

Interaction Studies

- Alpha-blocker(Tamsulosin 0.4mg)
- Udenafil 200mg

- CYP 3A4 inhibitor(Ketoconazole 400mg)
- Udenafil 100mg

- Fasting, Low-fat, High-fat
- Udenafil 200mg

- Alcohol 39g(0.088%)
- Udenafil 200mg

- Age(19~45 years vs. >65 years)
- Udenafil 100mg

Conclusions

Tamsulosin

- Standing SBP decreased 3.4%(4mmHg) after administration in combination with tamsulosin compared to tamsulosin alone.
- There were no significantly differences in C_{max}, AUC_{inf}, t_{max} and $t_{1/2}$.

Ketoconazole

- Coadministration of ketoconazole resulted in a 2-fold increase in AUC of Udenafil.
- There were no clinically significant differences for safety evaluations, when Udenafil was coadministered with ketoconazole.

Food

- T_{max} of Udenafil was increased under fed conditions.
- Although C_{max} was reduced by 20% in low-fat fed state, the bioavailability was not affected when taken with food.

Alcohol

- Udenafil did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 39g(0.088%)
- There were no clinically significant differences in PK and safety evaluations.

Elderly

- In elderly subjects, C_{max} and AUC decreased compared to young subjects.
- No dose adjustment was required in patients >65 years of age.

The reason why ocean is so salty…

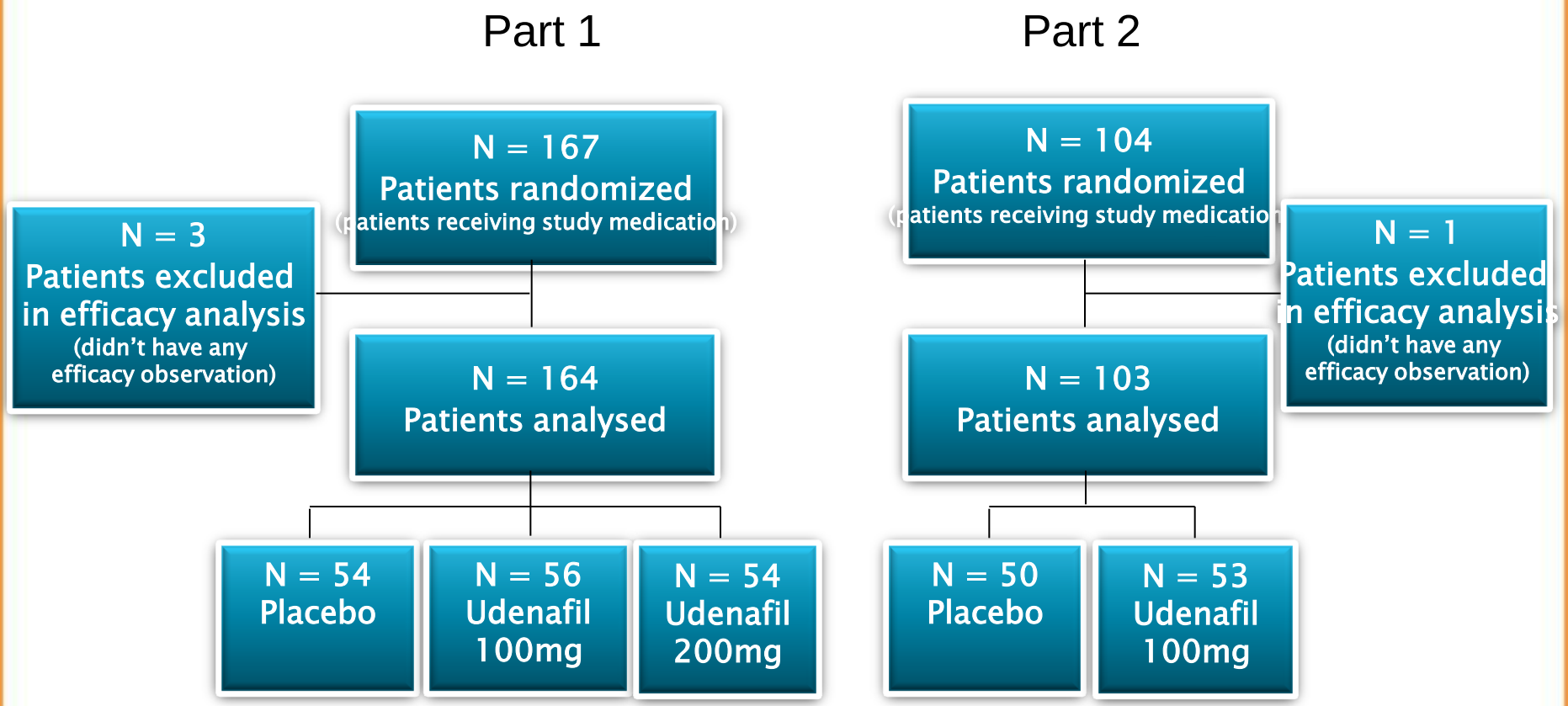
Clinical Study - *Phase 3*

- **Objectives**
  - To evaluate the efficacy, safety and tolerability of oral Udenafil in patients with ED
  - To examine the therapeutic effects of Udenafil on ED at 12 hours after dosing

- **Design**
  - double-blind, placebo-controlled, randomized, parallel group, fixed dose
  - Part 1 : 4 week treatment-free run-in period, 12 week treatment period (instructed to attempt the intercourse at 30min ~ 8hrs after dosing) dose levels - Udenafil 100mg, 200mg
  - Part 2 : 4 week treatment-free run-in period, 4 week treatment period (instructed to attempt the intercourse at 12hrs after dosing) dose levels - Udenafil 100mg

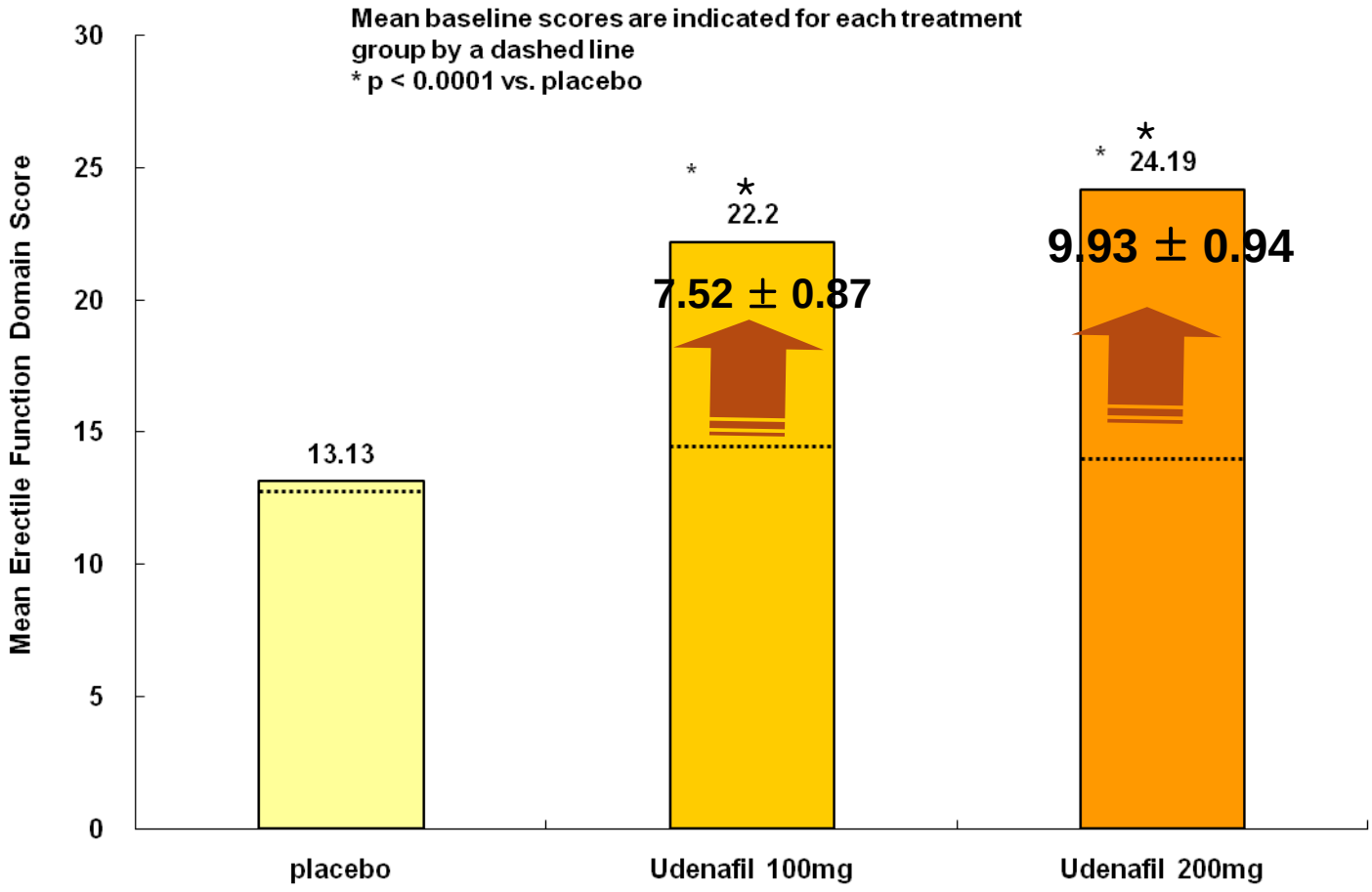
Clinical Study - *Phase 3*

- Total 271 patients were enrolled ;



Clinical Study - *Phase 3 ; part 1*

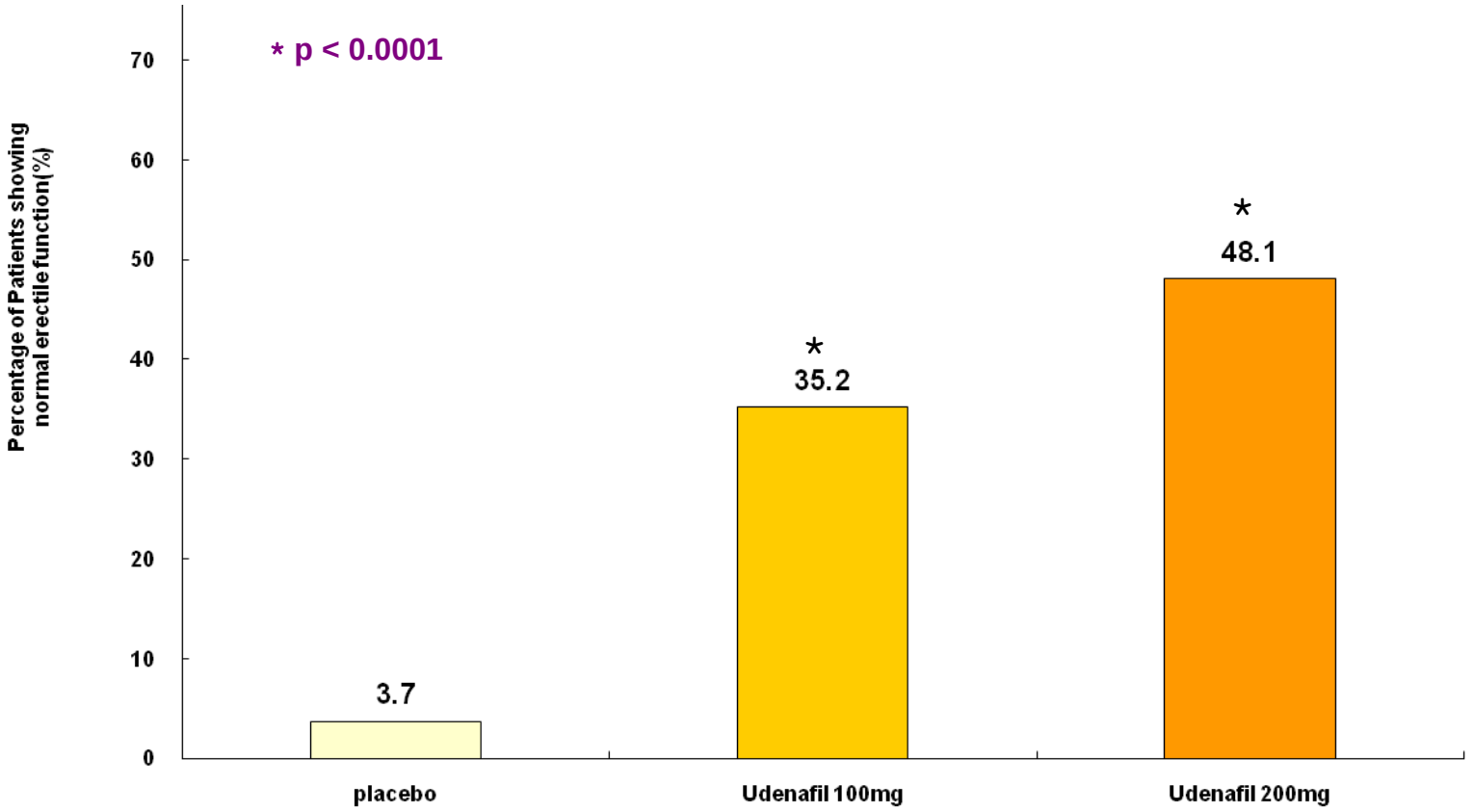
- IIEF EF domain



Clinical Studv - *Phase 3 : part 1*

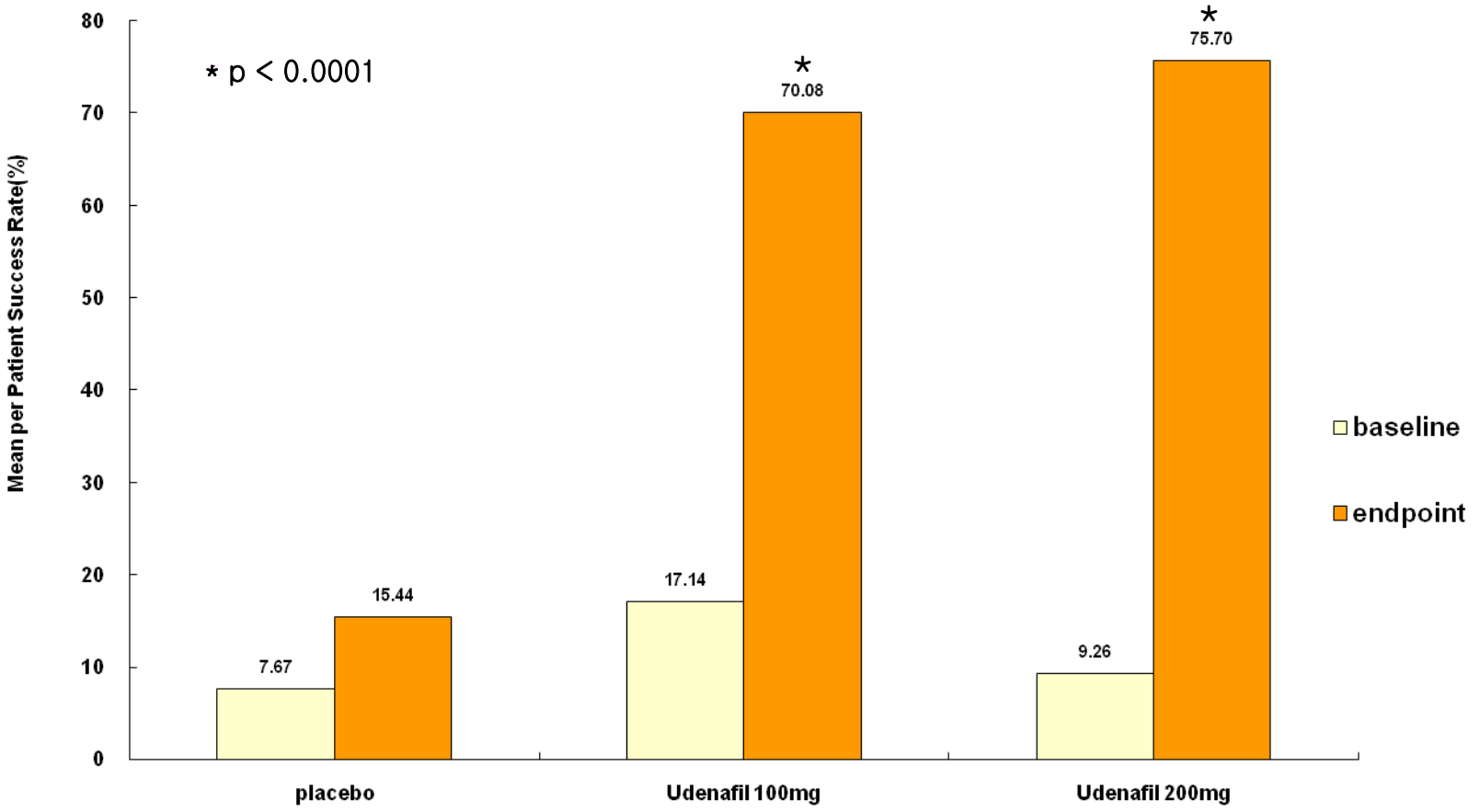
% of patients shift to normal at 12 weeks

; normal - EF domain of the IIEF ≥ 26



Clinical Study - *Phase 3 ; part 1*

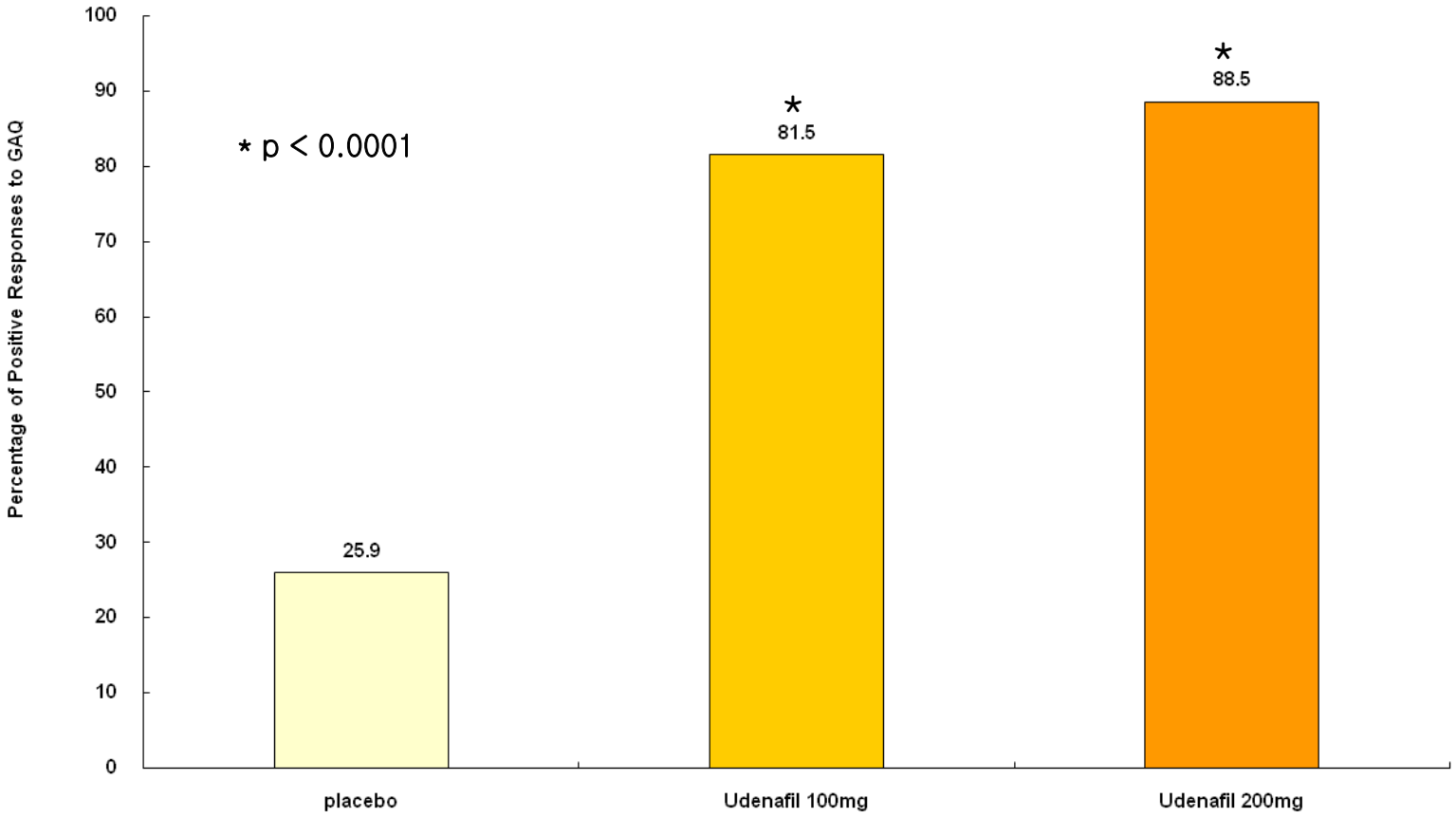
- SEP Q3



SEP Question 3 : Did your erection last long enough for you to complete intercourse with ejaculation?

Clinical Study - *Phase 3 ; part 1*

- GAQ



GAQ : Has the treatment you have been taking over the past 4 weeks improved your erection?

Clinical Study - *Phase 3 ; part 1*

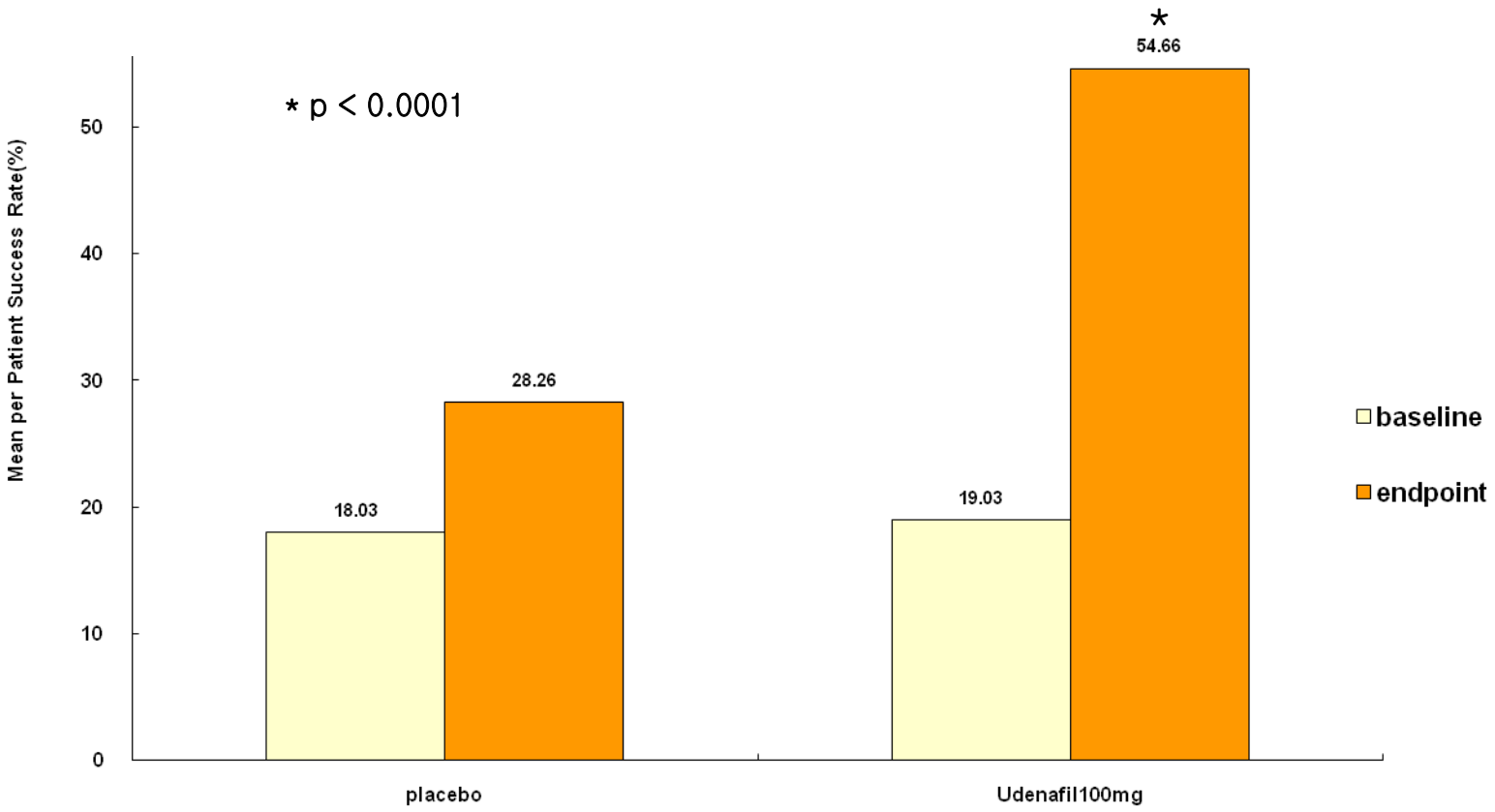
- Safety – Adverse Events (≥2%)

	No. of subjects with adverse event [%]		
		Dose of Udenafil	
	Placebo (n=54)	100mg (n=57)	200mg (n=56)
Flushing		6 [10.5%]	13 [23.2%]
Headache			5 [8.9%]
Nasal congestion		2 [3.5%]	4 [7.1%]
Ocular hyperaemia		2 [3.5%]	4 [7.1%]
Chest discomfort			3 [5.4%]
Dyspepsia			2 [3.6%]
≥ 1 Adverse events	3 [5.6%]	11 [19.3%]	21 [37.5%]

Clinical Study - *Phase 3 ; part 2*

7.5 ~ 12.5 hr postdosing

- SEP Q3



SEP Question 3 : Did your erection last long enough for you to complete intercourse with ejaculation?

Clinical Study - *Phase 3 ; part 2*

- Safety – Adverse Events

	No. of subjects with adverse event [%]	
	Placebo (n=50)	Udenafil 100mg (n=53)
Flushing		**1** [1.9%]
Headache	2 [4.0%]	**1** [1.9%]
Nasal congestion		**1** [1.9%]
Stomach discomfort		**2** [3.8%]
Toothache		**1** [1.9%]
Thirst		**1** [1.9%]
≥ 1 Adverse Events	2 [4.0%]	**7** [13.2%]

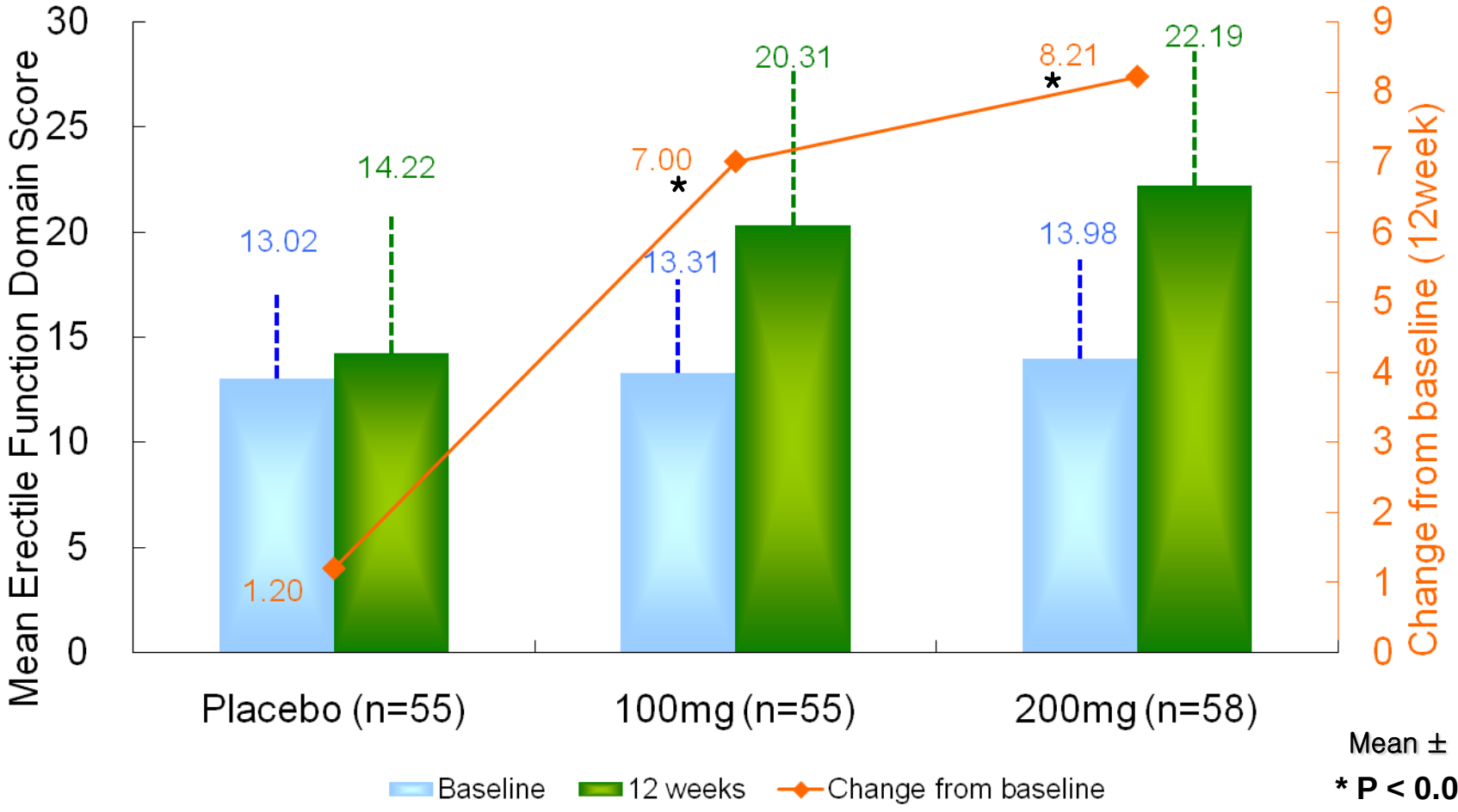
** No patients discontinued the study due to adverse events*

Clinical Study – *Conclusions*

- Udenafil 100, 200mg produced significant improvements in erectile function and improved rates of vaginal penetration, intercourse success, and overall satisfaction with sexual experience in a broad population of men with ED
- Udenafil was well tolerated with the most common treatment-emergent adverse events being flushing, headache, nasal congestion
- Udenafil 100, 200mg were well tolerated and significantly improved erectile function and intercourse success rate for patients with erectile function regardless of baseline severity

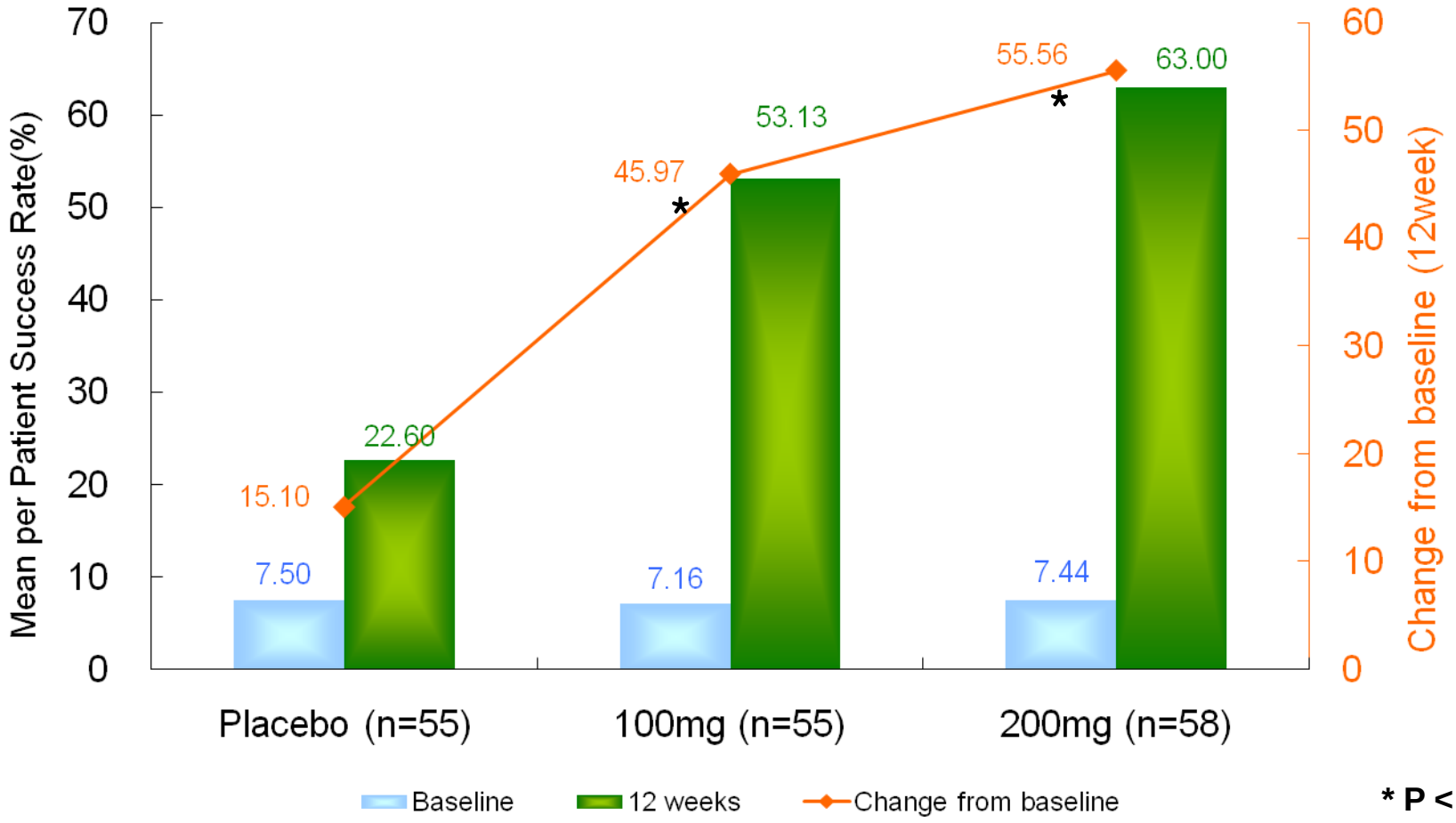
Effect of Udenafil for treatment of ED in Men with Diabetes

IIEF Erectile Function Domain (1)



SEP Q3 (Intercourse success rate)

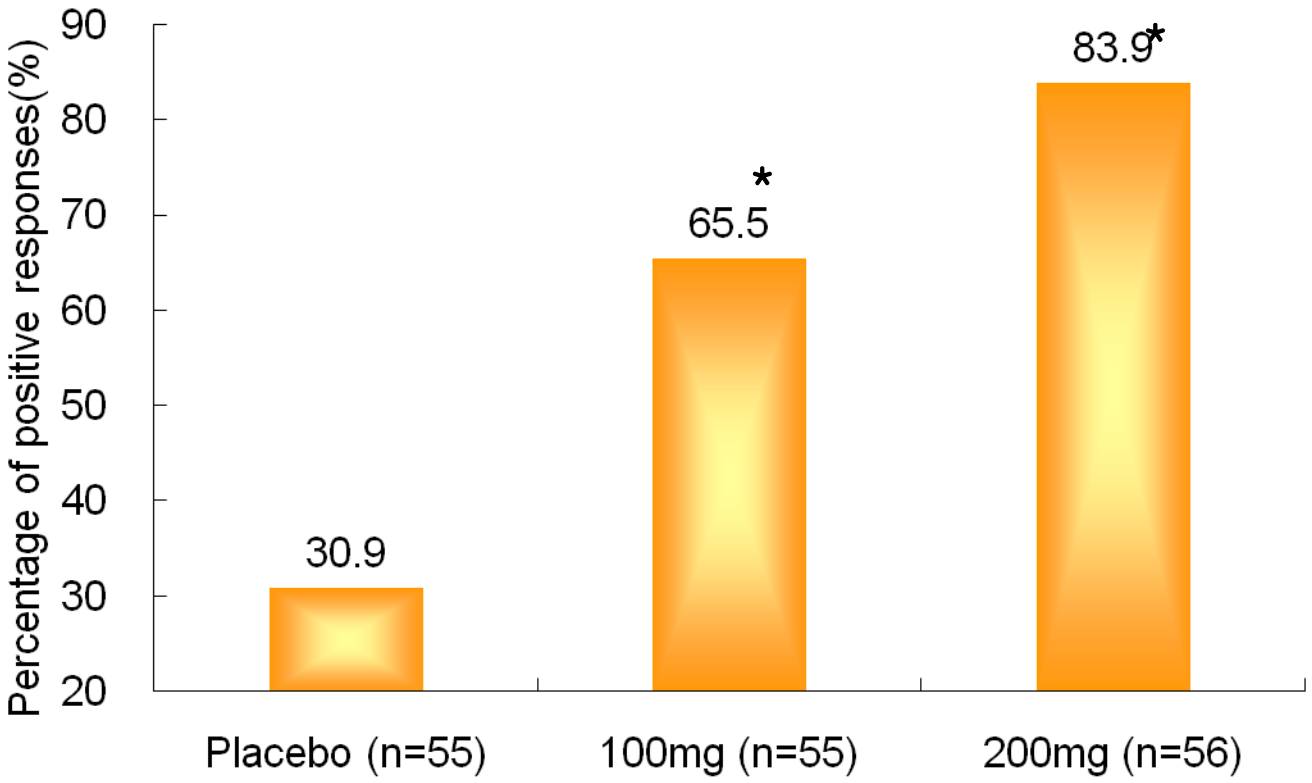
SEP Q3 : Did your erection last long enough for you to complete Intercourse with ejaculation?



*** P < 0.001**

Global Assessment Question

GAQ : Has the treatment you have been taking over the past 4 weeks improved your erection?



* P < 0.0001

Zydena®

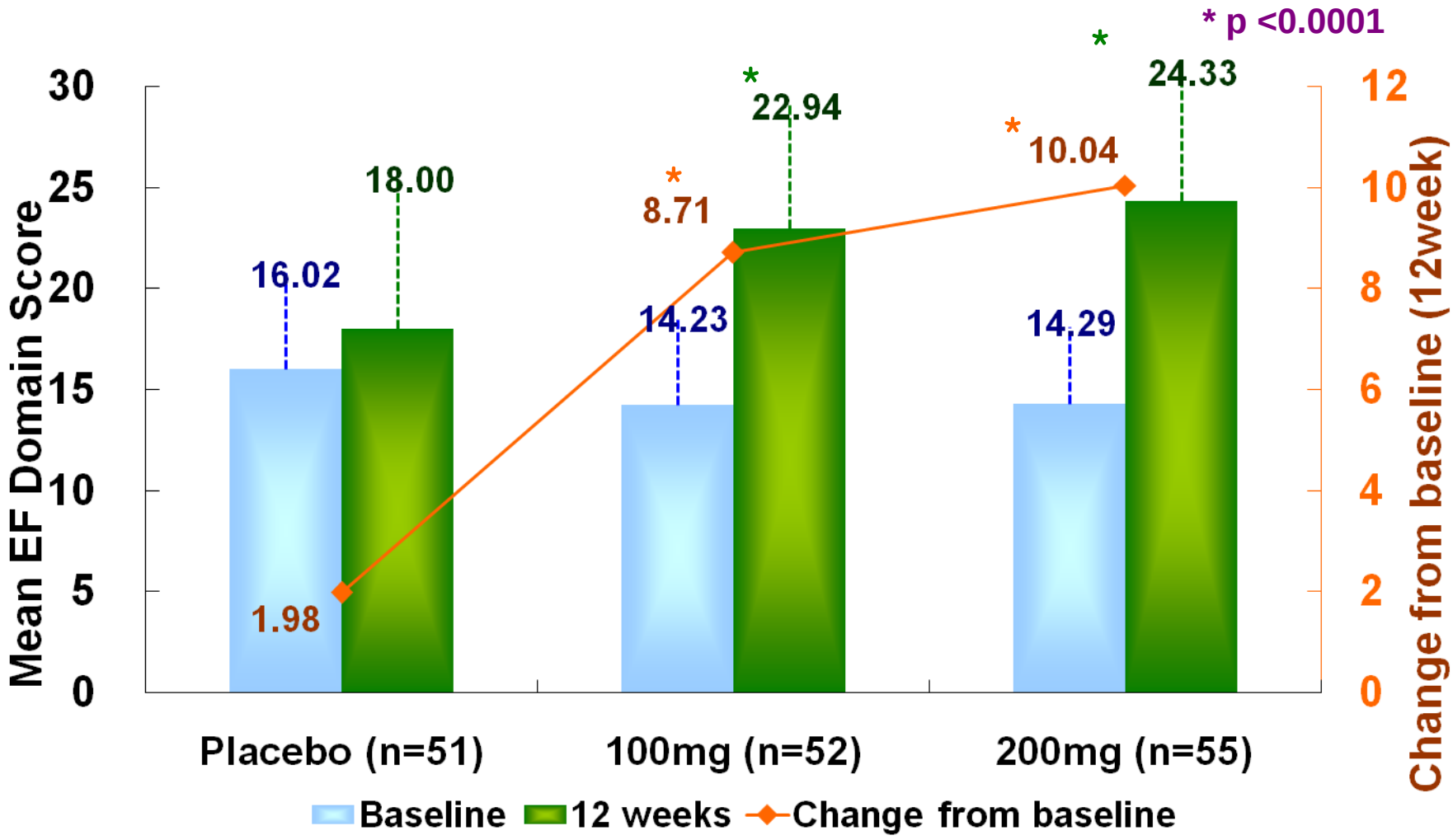
Dong-A Pharm. Co. Ltd.

Frequency of Drug-related AEs

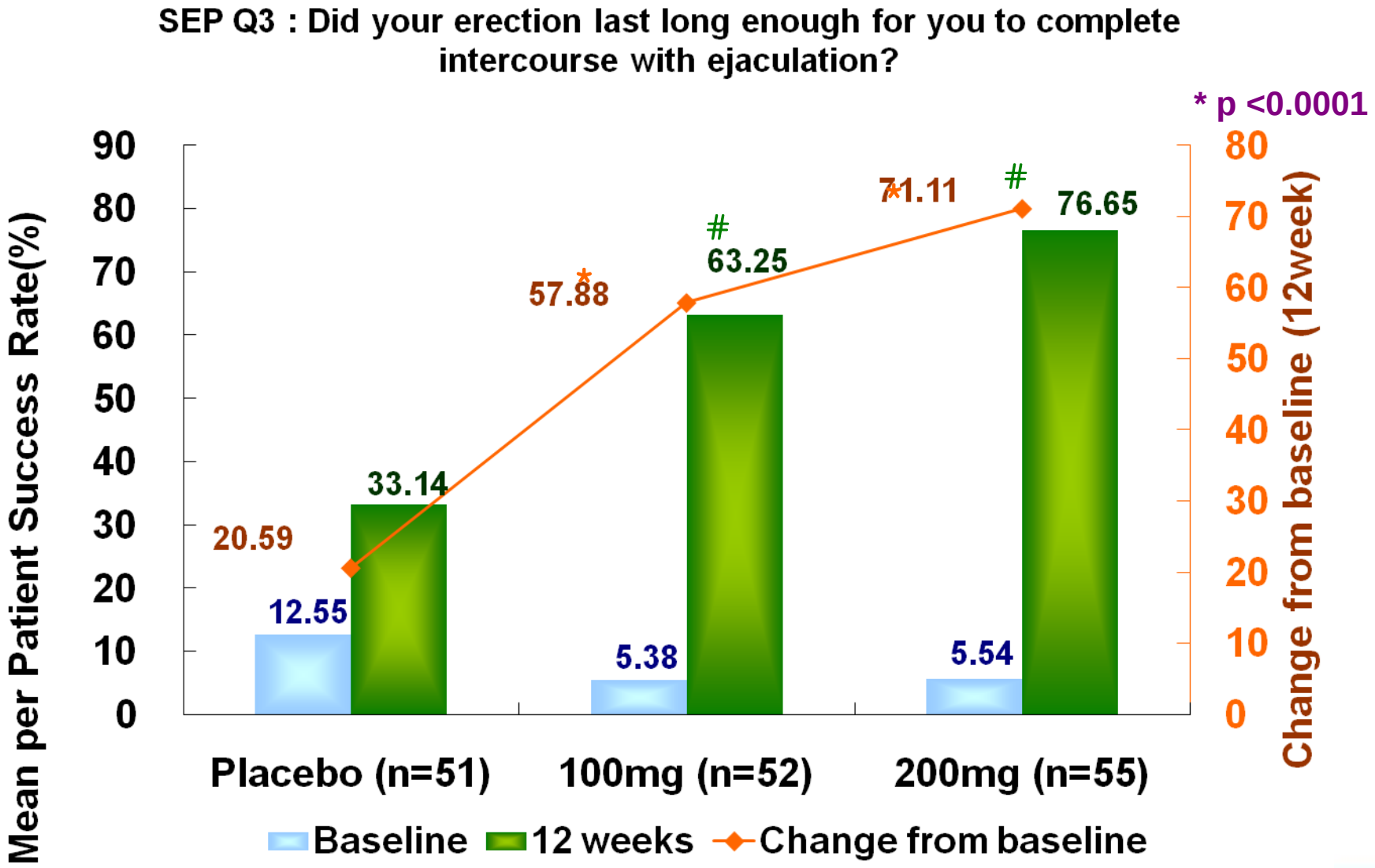
MedDRA Preferred Term	No. of subjects with Drug-related adverse event[%]		
		Dose of Udenafil	
	Placebo (n=55)	100mg (n=57)	200mg (n=58)
Flushing	1 [1.8%]	5 [8.8%]	7 [12.1%]
Headache		1 [1.8%]	3 [5.2%]
Nausea		1 [1.8%]	2 [3.4%]
Conjunctival hyperaemia	1 [1.8%]	1 [1.8%]	1 [1.7%]
Chest discomfort		1 [1.8%]	
Dizziness			1 [1.7%]
Dyspepsia			1 [1.7%]
Pruritus			1 [1.7%]
Total	2 [3.6%]	9 [15.8%]	13 [22.4%]

Effect of Udenafil on Hypertensive men with ED taking concomitant antihypertensive medication

IIEF EF Domain (1)



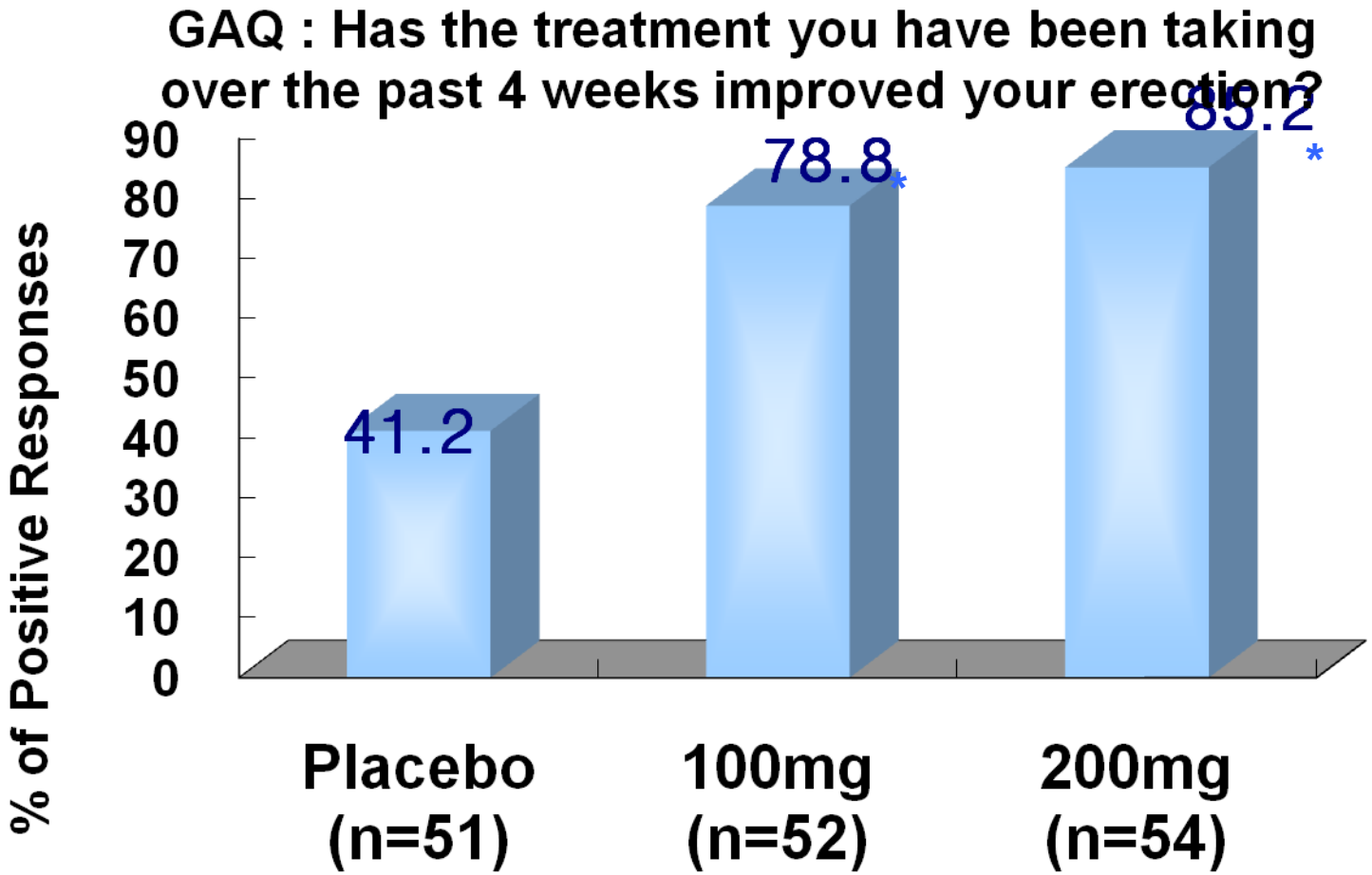
IIEF SEP Q3



Zydena®

동아제약

Global Assessment Question



* p <0.0001

† one subject's data was missing

Frequency of Drug-related AEs

MedDRA Preferred Term	No. of Subjects		
		Zydena®(Udenafil)	
	Placebo (n=54)	100mg (n=53)	200mg (n=57)
		Users (%), duplicated by items	
Flushing	1 (1.9)	3 (5.7)	3 (5.3)
Headache		1 (1.9)	5 (8.8)
Dyspepsia		1 (1.9)	3 (5.3)
Conjunctival hyperaemia		2 (3.8)	3 (5.3)
Chromatopsia			1 (1.8)
Total	1 (1.9)	5 (9.4)	9 (15.8)

Safety Comparison

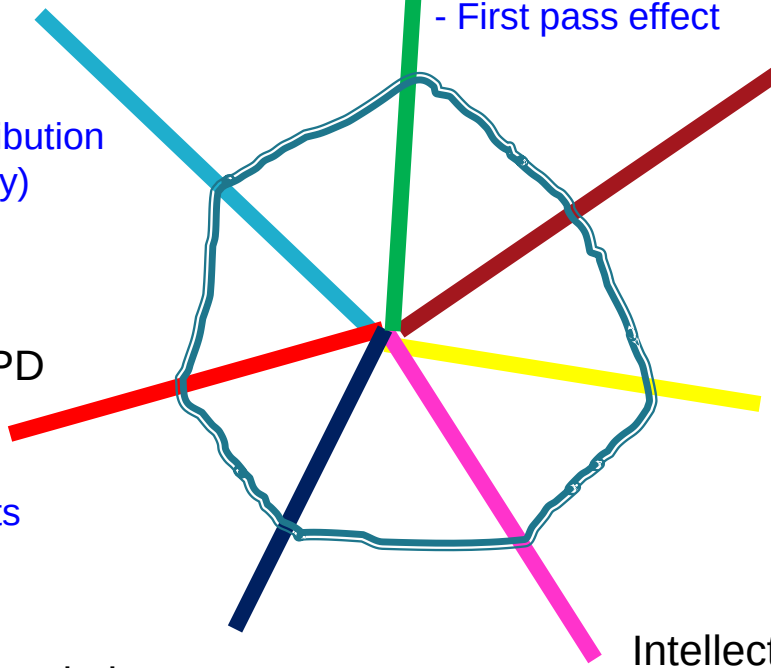
	Viagra N=734	Levitra N=2203	Cialis N=635	Zydena N=380
Headache	16%	15%	15%	7.6%
Flushing	10%	11%	2%	12.3%
Dyspepsia	7%	4%	10%	2.3%
Nasal Congestion	4%	9%	1%	2.3%
Urinary Tract infection	3%	-	-	-
Abnormal Vision	3%	-	-	-
Diarrhea	3%	-		-
Back pain	-	-	6%	-
Myalgia	-	-	3%	-
Pain in limb	-	-	3%	-
Dizziness	2%	2%	-	1%
Rash	2%	-	-	-
Accidental Injury	-	3%	-	-
Sinusitis	-	3%	-	-
Flu like syndrome	-	3%	-	-

Reviced data from company file

▪ 고려사항

- Facilitated Lead Optimization
- 전문 Biotech
- 개발/시장 전략
- CONSULTATION 활용 및 연구자 cross-talk
- 가치 부여
- Clumsy error – Tremendous efforts
- IP 및 구조 Release
- Racemate
- QT issue

▪ Facilitated Lead Optimization : Balanced, Best Profile



Oral Bioavailability
- Relevant Animal spp.
- predictable Human BA
- First pass effect

Physicochemical Properties
- Solubility/Stability
- Hygroscopicity
- LogP and tissue distribution
- Stereoisomer (chirality)
- Protein binding

PK and Metabolism
- Dosing freq. (eg.QD)
- No inhibit/induce CYPs
- No or diverse paths

Primary/Secondary PD
- nM potency
- Efficacy
- clear off-target effects

Toxicity
- Liver, Kidney, Muscle
- clear hERG/telemetry
- Geno-carcinotox
- Sufficient Safety margin

Synthesis, Formulation
- Pharmacoeconimics
- Tailored formulation

Intellectual Properties
- Clear IP (CoM, Process, Use, Extension)

▪ Repeated Trial & Error, Close collaboration among Design-Syn-Eval, Insight & Sense

專門 Biotech

- Dong-A PharmTech is a Korean pharmaceutical company focused on the worldwide development and commercialization of udenafil ex-Korea
  - It is a sister company to Dong-A Pharmaceutical, the largest drug company in Korea

DONG-A PHARM®

- Established in 1932
- Listed on Korean Stock Exchange
- Market value of ~US$750 million
- Developed and launched udenafil in Korea under the brand name Zydena®, using its internal R&D, manufacturing and sales force capabilities
- Retains Korean rights to udenafil

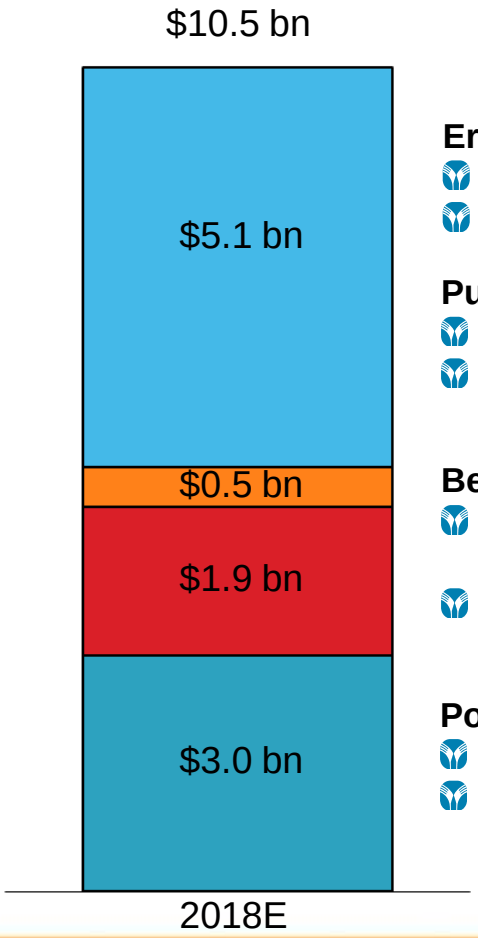
DONG – A PHARMTECH

- **Facilitated decision making & investm.**
- **Reduced risk of AE-related lawsuits**

- Outsourced expertises
- L/O deal experience
- Territory-based rights

■ 開發-市場 戰略

PDE-5i Worldwide Market Potential



Erectile Dysfunction (ED)
- Large and growing market
- Shift to long-acting

Pulmonary Arterial Hypertension (PAH)
- High unmet need
- Clear advantage over Revatio (3-times-a-day formulation of Viagra) due to once-daily dosing

Benign Prostatic Hyperplasia (BPH)
- Nearly 5 million men in US seeking treatment; synergies with ED
- Advantage over competitors due to once-daily dosing and side-effect profile

Portal Hypertension (PH)
- Underserved population with high unmet need
- European development partner to initiate clinical trials in Europe in 2007

Potential to be competitively positioned in large chronic indications given potential for once-daily dosing and superior side-effect profile

Is it true? And Considerable M/S can we garner?

ED Market Consists of Three Brands Differentiated By Duration and Tolerance

Long Acting

Short Acting

Cialis® (tadalafil) tablets

- Only product growing consistently in volume, share and price with 31% of sales
- Highest priced product with largest price increases
- Only long acting product with up to 36-hour duration
- Launched in 2003

VIAGRA® (sildenafil citrate) tablets

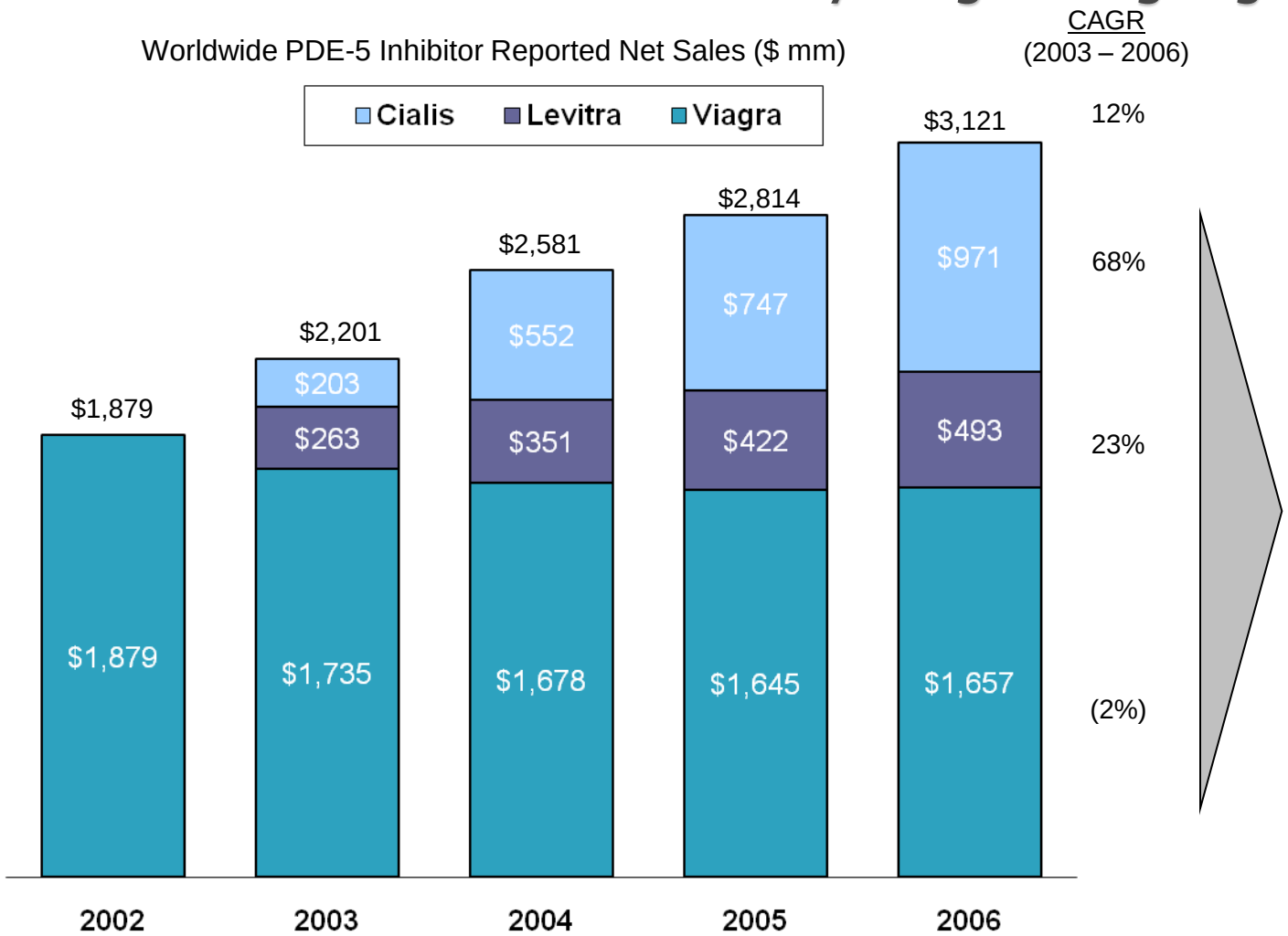
- Market leader with 53% of sales (2006)
- Losing global market share and unit volume but:
  - Maintaining sales levels through price increases
- Short acting product with up to 4-hour duration
- Launched in 1998

LEVITRA® (VARDENAFIL HCl)

- Sporadic volume and share growth with 16% of sales
- Lowest priced product on market
- Short acting product with up to 4-hour duration
- Launched in 2003

- Long acting is driving new scripts
- Long acting and adverse effects drive prescription switch
- No new products since 2003

Worldwide Sales Growth Driven by Long-Acting Segment



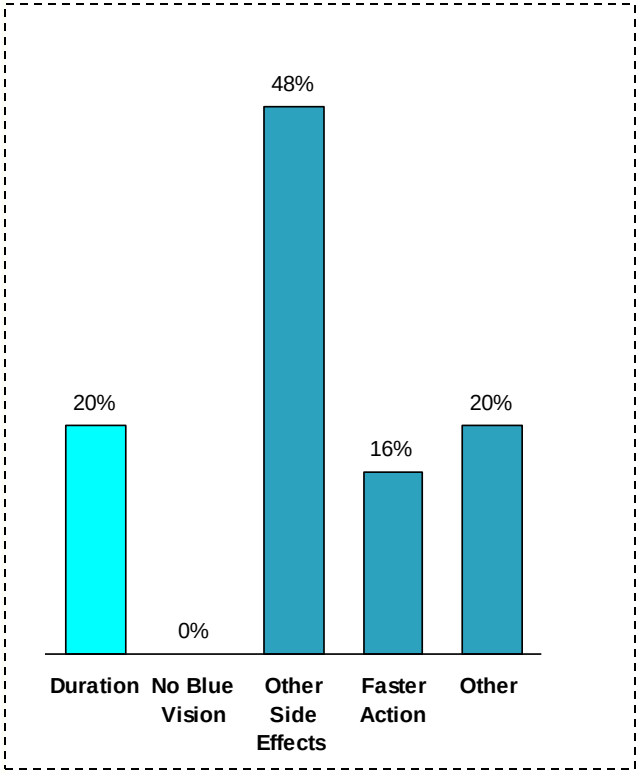
- Long acting product (Cialis) accounted for 84% of sales growth since end of 2003
- "Most preference studies have shown Tadalafil to be preferred"
- *International Journal of Impotence Research*, December 2006
- In 2006 Cialis grew +30% vs. ED market growth of 11%

Source: Lilly/ICOS 2006 Earnings Report, ICOS Annual Report 2004 & 2005; Pfizer 4th Qtr '06 Earnings Report; Pfizer Annual Reports 2004 & 2005; Bayer 3rd Qtr'06 Earnings Reports, Bayer Annual Reports 2004 & 2005; GSK Annual Reports 2004 & 2005 – Bayer & GSK results converted to US$ using 12/31/06 exchange rates; Dogrell, S. International Journal of Impotence Research: Dec 06.

Duration and Side Effect Profile Are Primary Reasons for Switching ED Medications

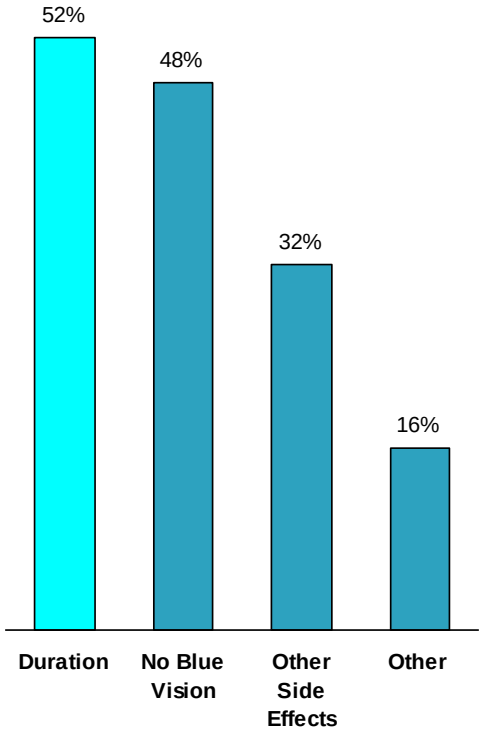
Long Acting

Advantages of new treatment over Cialis
Percent of Respondents

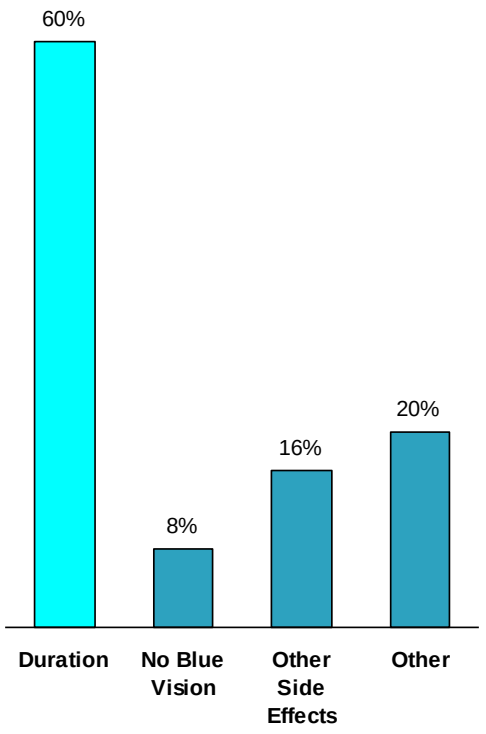


Short Acting

Advantages of new treatment over Viagra
Percent of Respondents



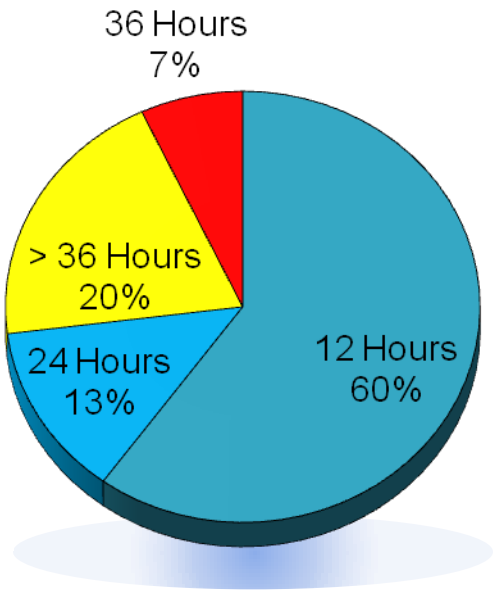
Advantages of new treatment over Levitra
Percent of Respondents



Source: Market research survey in September 2005 of urologists (n=10) and primary care physicians (n=15) who reported seeing a minimum of 10 ED patients per month

12-24 hours is Most Desirable Duration for Patients Considering a Long Acting PDE-5I

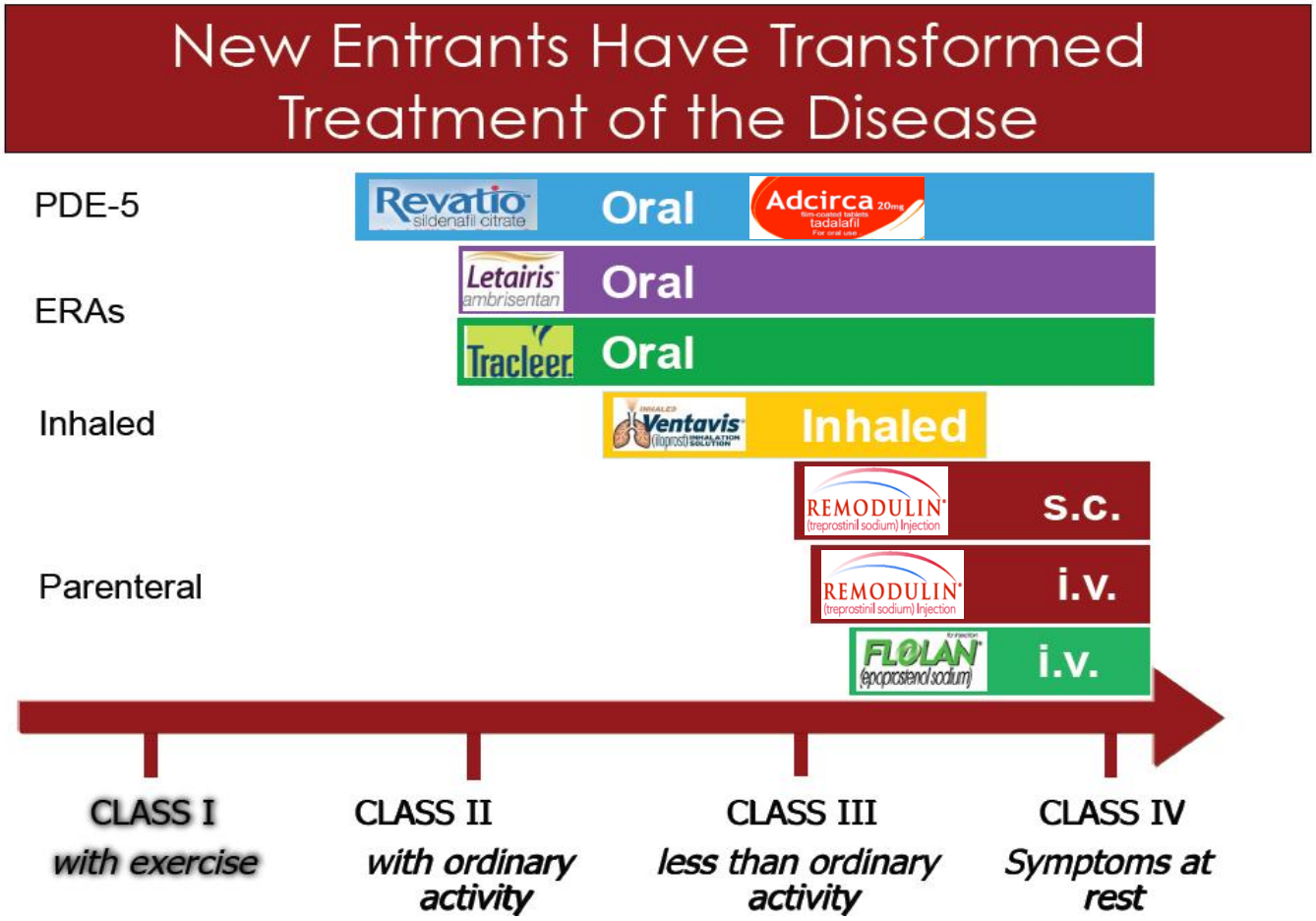
Most Desirable Duration of Action
% of Respondents



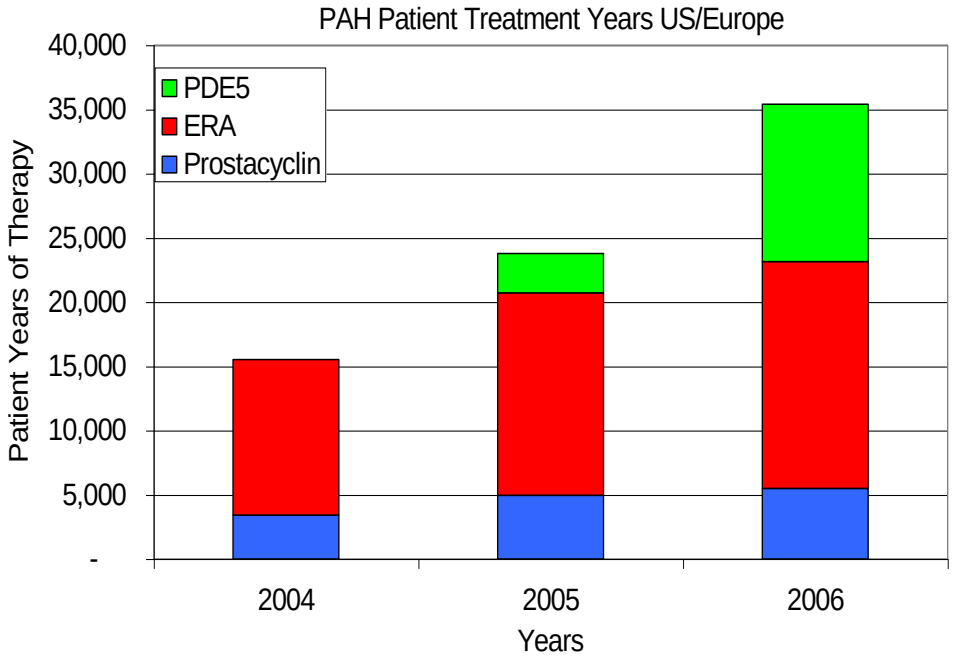
Patients seek 12 to 24 hour duration in an ideal PDE-5 inhibitor

Market Positioning is critical.
What's the future after expiry of Viagra after 2012? Still ED market be lucrative? Otherwise, what?

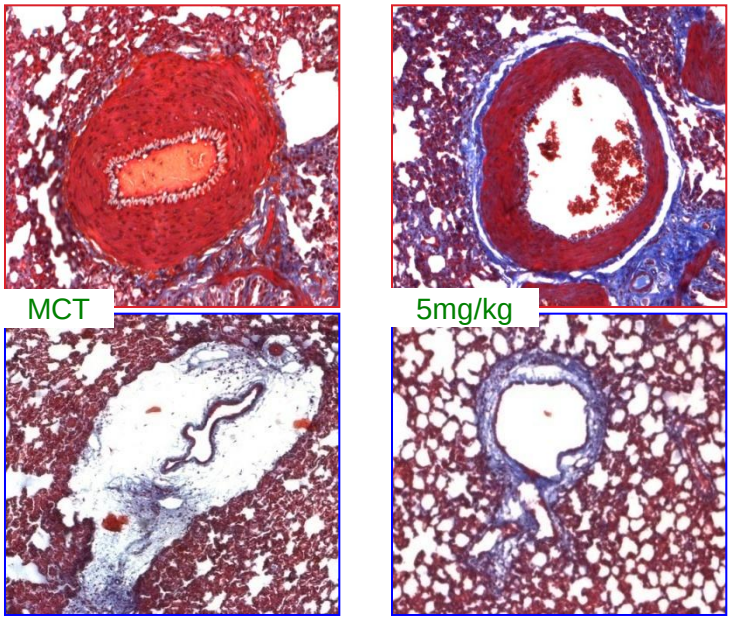
PAH Treatment Pathways/Products



Impact of PDE5 on PAH Market



Micrographs of pulmonary arterial vessels



Udenafil also shows efficacy
In animal models

- There are four potential reasons to believe that PAH patient years of therapy will continue to expand over the next few years:
  - PDE 5 inhibitors (Revatio) have been readily adopted as 1st line therapy due to their comparable efficacy (6 MWD) and lack of liver toxicity.
  - Prostacyclin and ERA products have dramatically increased the 3 year survival rate (# of pts)
  - Actelion has invested significant effort for early diagnos(# of pts)
  - The advent of relatively cheap & safer PDE 5 therapy replace ERA and prostacyclin therapies

However, in Actual Market….

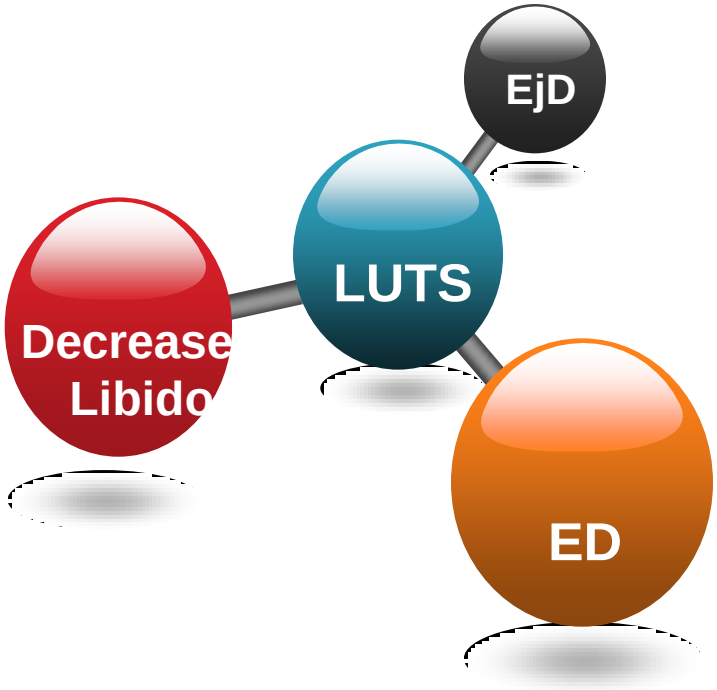
Hard to penetrate the PAH market even with more favorable profiles

	2009. 1Q	2010. 1Q	
Bosentan (Tracleer)	306	352	mil$
Ambrisentan (Letairis)	39	55	
Sildenafil (Revatio)	113	114	mil$
Tadalafil (Adcirca)	3Q 1.5	5	

So, we suspend WW program and are pursuing domestic market for Korean patients

Then, What?

LUTS-BPH and LUTS-SD Comorbidity



PDE5i monotherapy or PDE5I+AB is a promising option for future therapy

Current Therapies
- AB, 5ARI, Others
- AB+5ARI (CombAt study)
  (Minimal) additional benefit
  Increase in severity of MSD
  Useful for Obstructive LUTS (Enlarged Prost)

Future
-After 2014, 2 brand left, tadalafil and duodart
-PDE5i mono for ED/BPH comorbidity
-AB+PDE5i combo for BPH
-Cross-Rx and cross-advertisement
-Reimbursement and Pricing critical by area

-Reasonable pricing and reimbursement can make **Udenafil a rule maker**

▪ CONSULTATION 활용 및 연구자 cross-talk

- Use Top Experts in the field
- Best Clinicians are not always Best PIs
- News : Seminars (>1-2 mo), Manuscripts (>6 mo), Publications (>2-3 yrs)

- Early participation of clinicians in the explorative R&D
- Active involvement of preclinical expertise in clinical stages

- ED : HPN/IG/RS, PE : MW/FG (임상 개발경험과 지식 및 통찰력)

- 가치부여

  - Molecule nature / Value creation
  - Differentiation from competitors
  - New use and repositioning
    (ex. Achlasia, Post-ERCP pancreatitis prevention, Combo with chemo for brain tumor..)

- Clumsy errors

  - Immature animal use
  - P1 volunteers, leading questions

- IP and Structure Release

  - Don’t disclose as late as you can

- Racemate

We can develop a racemate when
- there's cross-conversion
- indistinguisable (target and off-target effects)
- with plausible reasons eg. Technical, economical difficulties

Udenafil
- Indistinguishable
- Question submitted

Question to the Division

Does the division agree that the studies and data presented below are sufficient to support the on-going development of racemic udenafil for the planned NDA for the treatment of erectile dysfunction?

- Stereochemistry
- Stability of R-,S-Udenafil (- in solution, optical rotation)
- Nonclinical (vitro data, single enantiomer PK in animals with metabolite)
- Human biomaterials (protein binding, Caco-2 permeability, hepatic meta., CYP inh)
- Clinical (stereoselective bioanalysis efforts)

We also refer to your correspondence dated December 23, 2008, requesting the Division's concurrence whether the studies and data submitted are sufficient to support the ongoing development of racemic udenafil for a planned NDA submission.

We have completed the review of your submission, and we have the following response to your question "***Does the Division agree that the studies and data presented are sufficient to support the on-going development of racemic udenafil for the planned NDA for the treatment of erectile dysfunction***"?

We concur that the studies and data submitted to date are sufficient to support the ongoing development of racemic udenafil. However, the following information should be provided in the NDA submission:

▪ QTc issue

- ICH S7B, ICH E14 (TET), Intense ECG monitoring, <10msec, Risk-Benefit Evaluation
- Many talks, most of them are not experts

Results of Viskin Trial (2005)

4 tracings shown to 4 groups –
2 normal QT and 2 had LQTS

	% correct
QT experts:	96
Electrophysiologists:	62
Cardiologists:	22
Non-Cardiologists:	21

- Udenafil, a PDE5i possessing peripheral vasodilator, drops minimal BP and increases HR
  Thus QTc can be increased which might be more prominent with alcohol or 3A4 inhibitors
  QT inversely varies with HR.

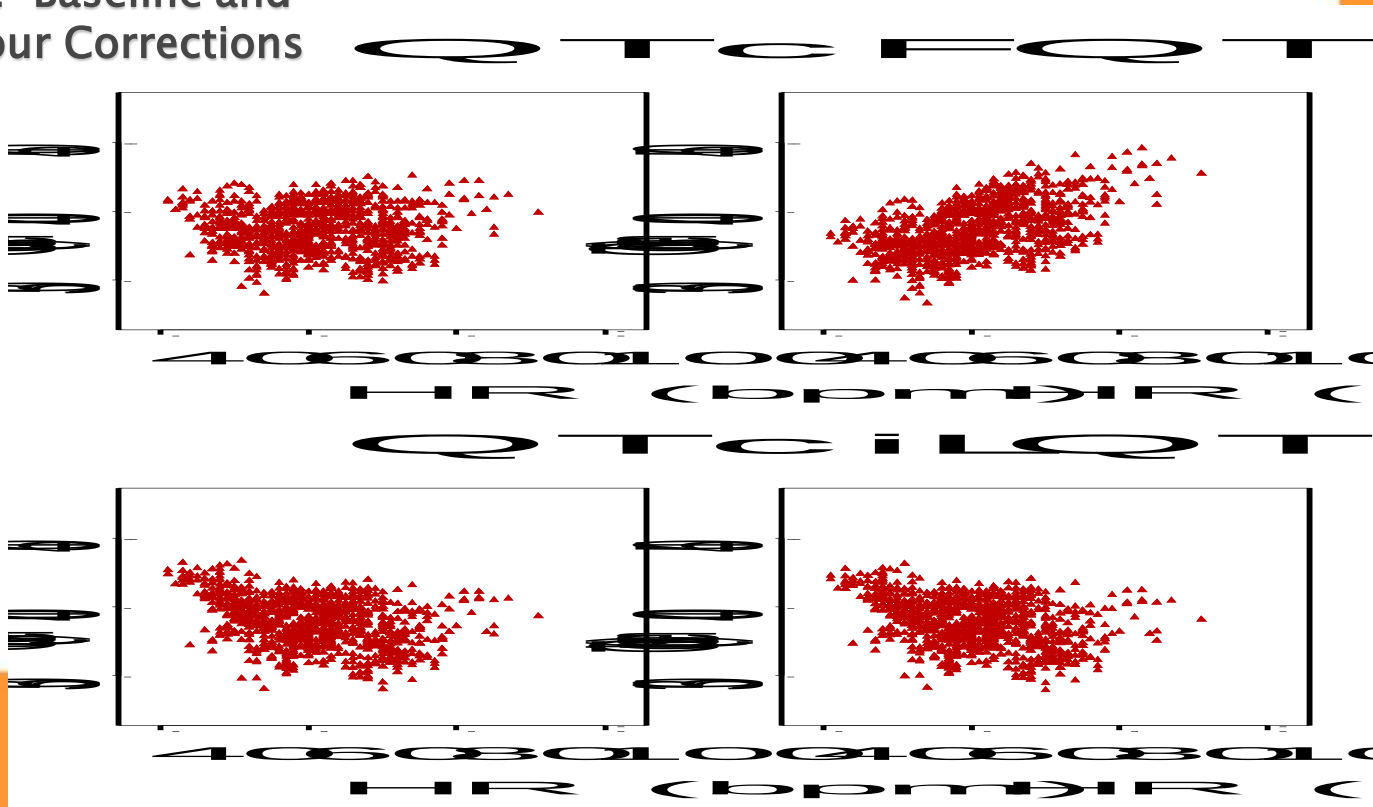
How to correct HR effect?

TET: How to Correct for HR Effect

from J. Morganroth PT (2006)

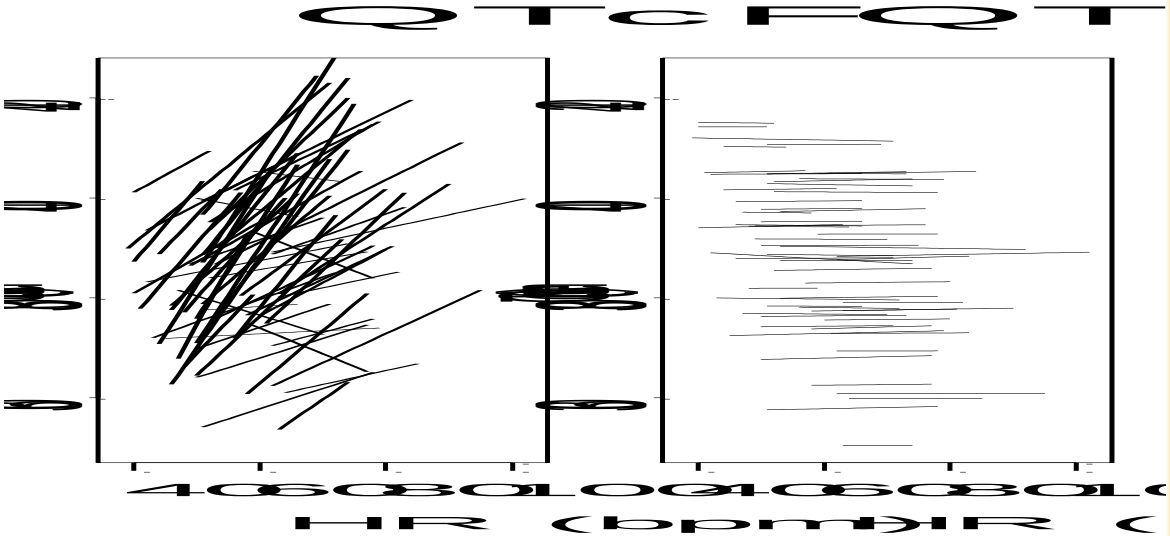
- Must concentrate on corrected QT since QT varies inversely with heart rate. QTcB and F are mandatory in submissions despite QTcB clearly less accurate. **QTcI "most suitable"** [line 484]
- To obtain a QTcI need at least **35-40 ECGs before any treatment contamination** so with 3 ECGs per time point need at least 14 time points at baseline
- Why is QTcI better:

Population QTc vs HR: Baseline and Placebo Data Using Four Corrections

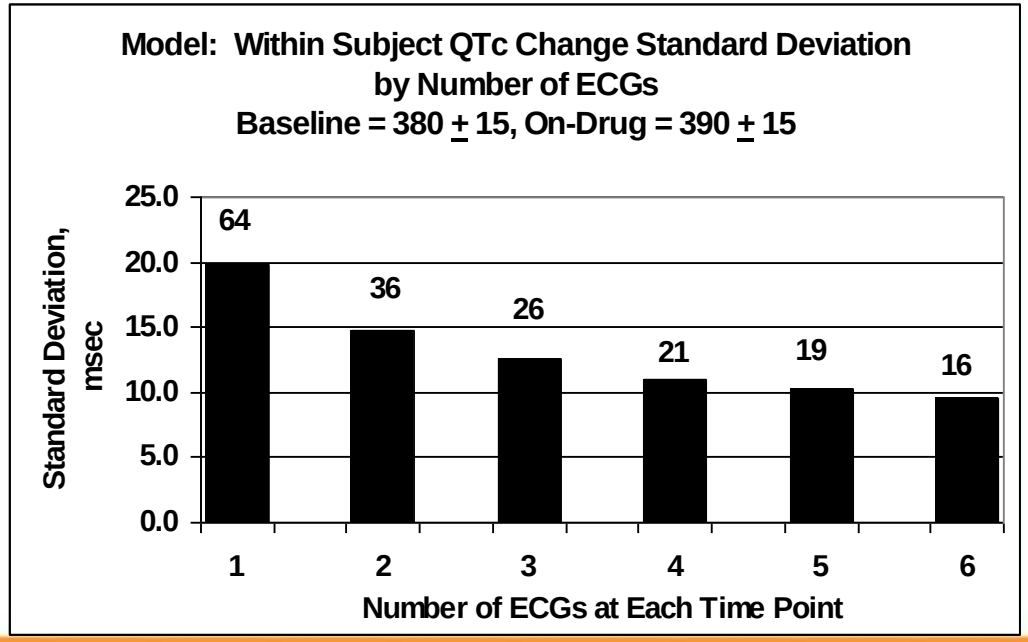


Zydena®

Individual Slopes of QTc vs HR: Baseline and Placebo Data Using 2 Corrections



How many ECGs to get at each Time Point?



감사합니다 !