Suppressive Therapy with Valtrex® (valacyclovir HCl) Caplets to Reduce the Frequency of Transmission of Genital Herpes

GlaxoSmithKline NDA 20-550/S-019

Antiviral Drugs Advisory Committee Meeting

May 14, 2003

Sponsor's Presentation

- **Introduction**
  - David M. Cocchetto, Ph.D.
- **Study Design, Methods, and Results**
  - Stuart M. Harding, M.D.
- **Concluding Remarks**
  - Clarence L. Young, M.D.

Current Approaches to Reduce Transmission of Genital Herpes

- Abstinence from sexual activity
- Avoidance of sexual contact during symptomatic episodes of genital herpes
- Use of condoms during sexual contact (even if symptoms are absent)

However:

- These approaches are incompletely effective
- No prophylactic vaccine or microbicide is available

Therefore, an unmet need exists for additional approaches to reduce transmission of genital herpes

Current FDA-Approved Uses of Valtrex

- Treatment of herpes zoster (shingles)
- Treatment of herpes labialis (cold sores)
- Genital Herpes
  - Treatment of initial episode
  - Treatment of recurrent episodes
  - Suppression of recurrent episodes

History of Study HS2AB3009

- 1995: initial dialogue about study design among GSK, clinical investigators, and DAVDP
- Sept 1996: face-to-face meeting to discuss draft protocol, patient population, and endpoints
- Sept 1997: final protocol
- Feb 1998 to July 2001: enrollment period
- March 2002: last subject completed study
- October 31, 2002: sNDA submitted to DAVDP

Pre-Study Guidance from FDA to GSK

Guidance # 1:

- Primary endpoint should be acquisition of clinically symptomatic, laboratory-confirmed genital herpes in the susceptible partner
- Study should yield "strong" evidence of efficacy

Resolution:

- We adopted this primary endpoint and designed the study to detect a 75% reduction in transmission of genital herpes

Pre-Study Guidance from FDA to GSK

Guidance # 2:

- A robust analysis of safety is required for Valtrex in this relatively healthy population

Resolution:

- Clinical safety data were collected in study HS2AB3009 for 743 patients receiving Valtrex for 8 months
- Safety data have been collected in other clinical studies of suppressive therapy (over 1,500 patients receiving Valtrex for 6-12 months)

Pre-Study Guidance from FDA to GSK

Guidance # 3:

- It is important to assure that Valtrex is studied in addition to safer sex counseling and condoms

Resolution:

- The study provided all patients with safer sex counseling and encouraged use of condoms during all sexual acts

Proposed Labeling

INDICATIONS AND USAGE:

Genital Herpes: Valtrex is indicated for the treatment or suppression of genital herpes in immunocompetent individuals and for the suppression of recurrent genital herpes in HIV-infected individuals.

Reduction of Transmission During Suppressive Therapy: **Valtrex is indicated to reduce the risk of transmission of genital herpes with the use of suppressive therapy. Safer sex practices should be used with suppressive therapy.**

(*Clinical Trials* section of labeling contains the description of study HS2AB3009)

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Study HS2AB3009
A Placebo-controlled Evaluation of Valtrex® for the Prevention of HSV-2 Transmission in Heterosexual Couples

Stuart M. Harding, M.D.

Director, Anti-Infectives

Clinical Development & Medical Affairs

GlaxoSmithKline

Opening Remarks

Scope of Presentation

- Rationale
- Design Considerations
- Study Methods
- Results
- Safety
- Conclusions

Rationale

- Valtrex suppresses recurrences of genital herpes[1]
  - Transmissions may occur in the absence of lesions[2]
  - HSV-2 shedding is the source of transmissible infection[3,4]
- Valtrex reduces viral shedding[5]

1. Reitano M, et al. JID 1998;178:603-610.
2. Mertz G, et al. Ann Intern Med 1992;116:197-202.
3. Brown Z, et al. NEJM 1991;324:1247-1252.
4. Koelle D, et al. JAC 2000;45:T3 1-8.
5. Wald A, et al. ICAAC 1998;Abstr H-82.

Scope of Presentation

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- **Design Considerations**
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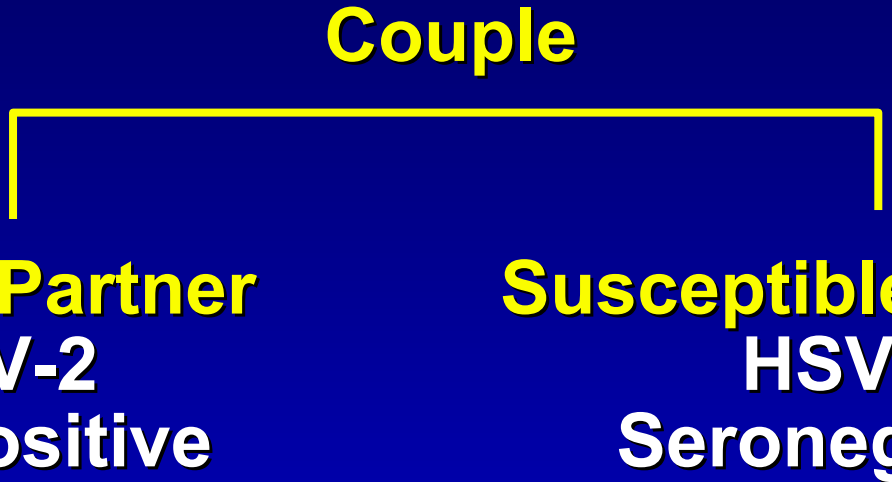
Design Considerations

- Study Population
- Dose and Duration of Dosing
- Sample Size
- Stratification
- Counseling
- Treatment of Episodes

Study Population



- Source partner suitable for suppressive therapy
- Susceptible partner monitored for acquisition of HSV
- Heterosexual partners in a stable monogamous relationship

Dose and Duration of Dosing

- Source partner allocated Valtrex or Placebo
- Valtrex 500mg once daily[1]
  - ≤ 9 episodes per year
- 8 months duration[2,3]
  - study procedures
  - partner switching
  - reduction in transmissions with time

1. Reitano M, et al. JID 1998;178:603-610.
2. Corey L, et al. JAMA 1999;282:331-340.
3. Wald A, et al. JAMA 2001;285;3100-3106.

Sample Size

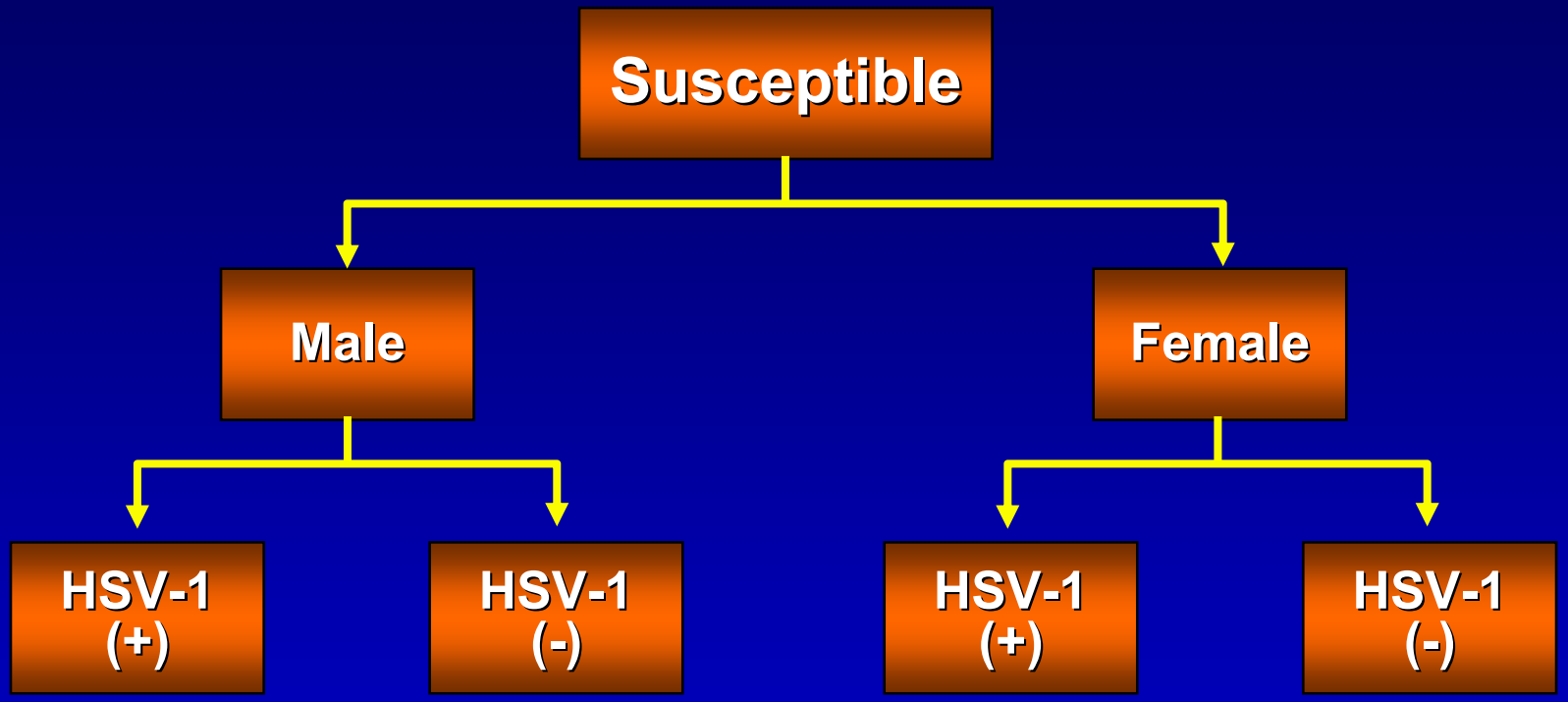
Transmissibility of HSV-2 variable

Assumptions for the sample size calculation:

- Prior studies showed ~3.5-10% acquisitions per year[1-3]
- Our assumption: 3% on placebo, with 75% reduction on Valtrex
- Goal: 28 clinical acquisitions for 90% power
- Number of couples required = 1,500

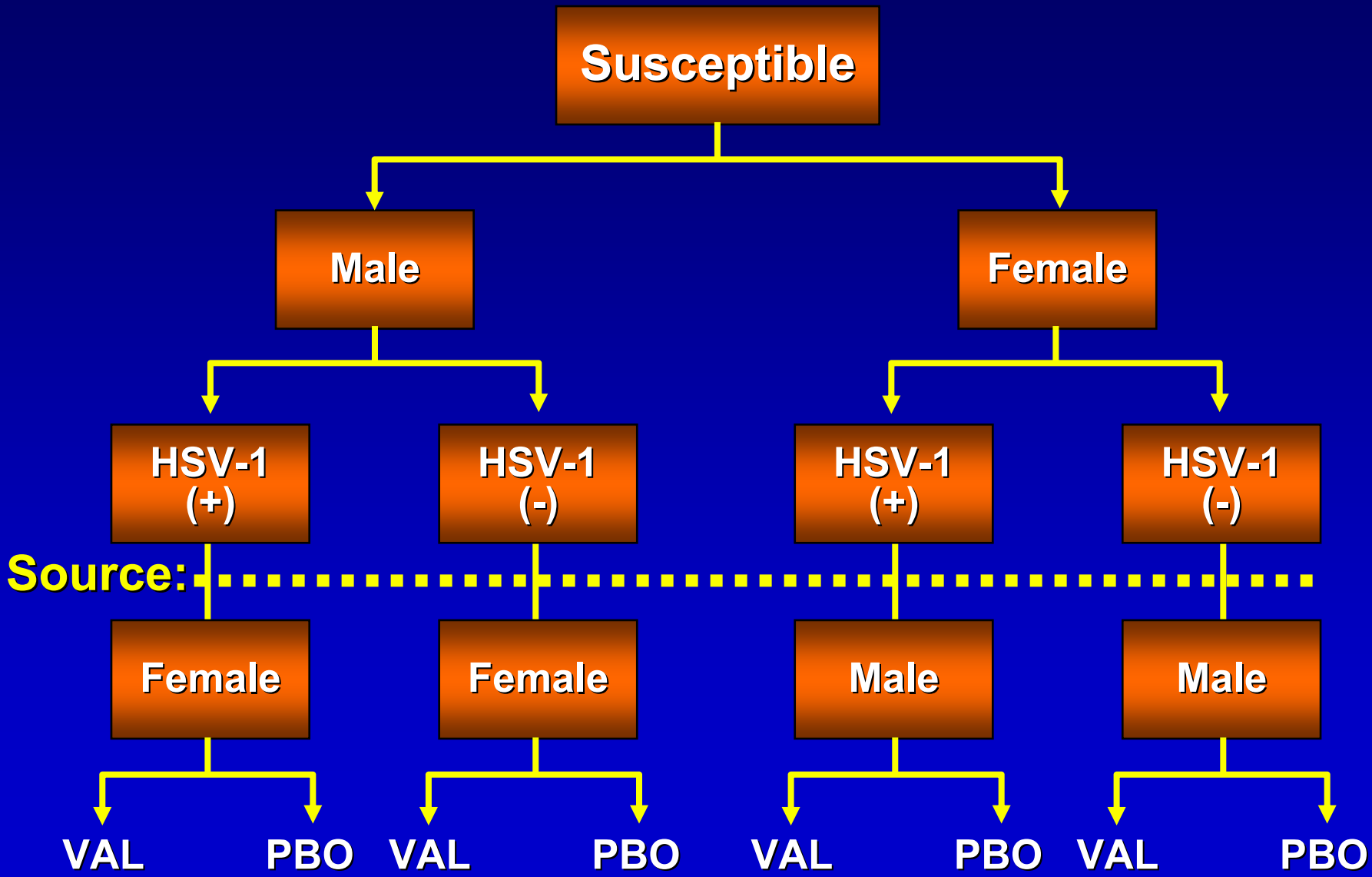
1. Bryson Y, et al. JID 1993;167:942-946.
2. Mertz G, et al. Ann Intern Med 1992;116:197-202.
3. Corey L, et al. JAMA 1999;282:331-340.

Stratification



Mertz G, et al. Ann Intern Med 1992;116:197-202.
Corey L, et al. JAMA 1999;282:331-340.
Wald A, et al. JAMA 2001;285:3100-3106

Randomization



Counseling

- Given at entry to the study and monthly
  - AMA[1] booklet distributed to all participants
- Principles of Safer Sex
  - avoid sex when signs or symptoms
  - use condoms for every sexual act (condoms available free at each site)

1. Amer Med Assn 1997.

Treatment of Episodes Source Partner

- Valtrex, 500mg twice daily for 5 days[1,2]
- Couples continued in the study

1. Spruance SL, et al. Arch Intern Med 1996;156:1729-1735.
2. Tyring SK, et al. Arch Dermatol 1998;134:185-191.

Scope of Presentation

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- **Study Methods**
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Study Schedule

Monthly clinic visits:

- Diary card review
  - genital herpes signs and symptoms
  - sexual contacts, including condom use
  - adverse events
  - concurrent medications
- Safer sex counseling, condoms offered
- Blood draw for serology
- Drug accountability

Suspected First Episode Of Genital Herpes: Susceptible Partner

- Clinic visit on Days 1, 5 and 10 (physical exam, HSV culture, PCR and serology)
- Subjects treated with open label Valtrex at approved dose
- If laboratory confirmed, subjects were considered to have completed the study

Primary Endpoint

- Acquisition of symptomatic genital herpes infection
  - Discussed and agreed prospectively among FDA, Investigators, and GSK
  - Determined by signs and symptoms of genital herpes
  - Confirmed by laboratory findings (culture, PCR and/or serology for HSV-2)
- Confirmed by Endpoints Committee

Endpoints Committee

- To determine if the case qualified as an acquisition of symptomatic genital herpes infection (primary endpoint)
- Committee blinded to treatment groups
- Followed written guidelines

Secondary Endpoints

Susceptible partners:

- Time to acquisition of symptomatic genital herpes infection
- Proportion with, and time to, overall acquisition

Source partners:

- Time to first recurrence of genital herpes
- Effect on viral shedding

Secondary Endpoints
Other

Susceptible partners:

- Proportion with, and time to, HSV-2 seroconversion
  - Proportion with, and time to, asymptomatic HSV-2 seroconversion
- Proportion with clinical evidence of a first episode of HSV-1

Source partners:

- Time to first oral HSV outbreak

HSV-2 Shedding Substudy

- Conducted in a subset of subjects enrolled in the main study
- 89 source partners from 3 US sites
- Participated for 60 days
- Daily genital swabs for HSV-2 PCR
- Additional swab of lesion if present

Scope of Presentation

- Rationale
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- **Results**
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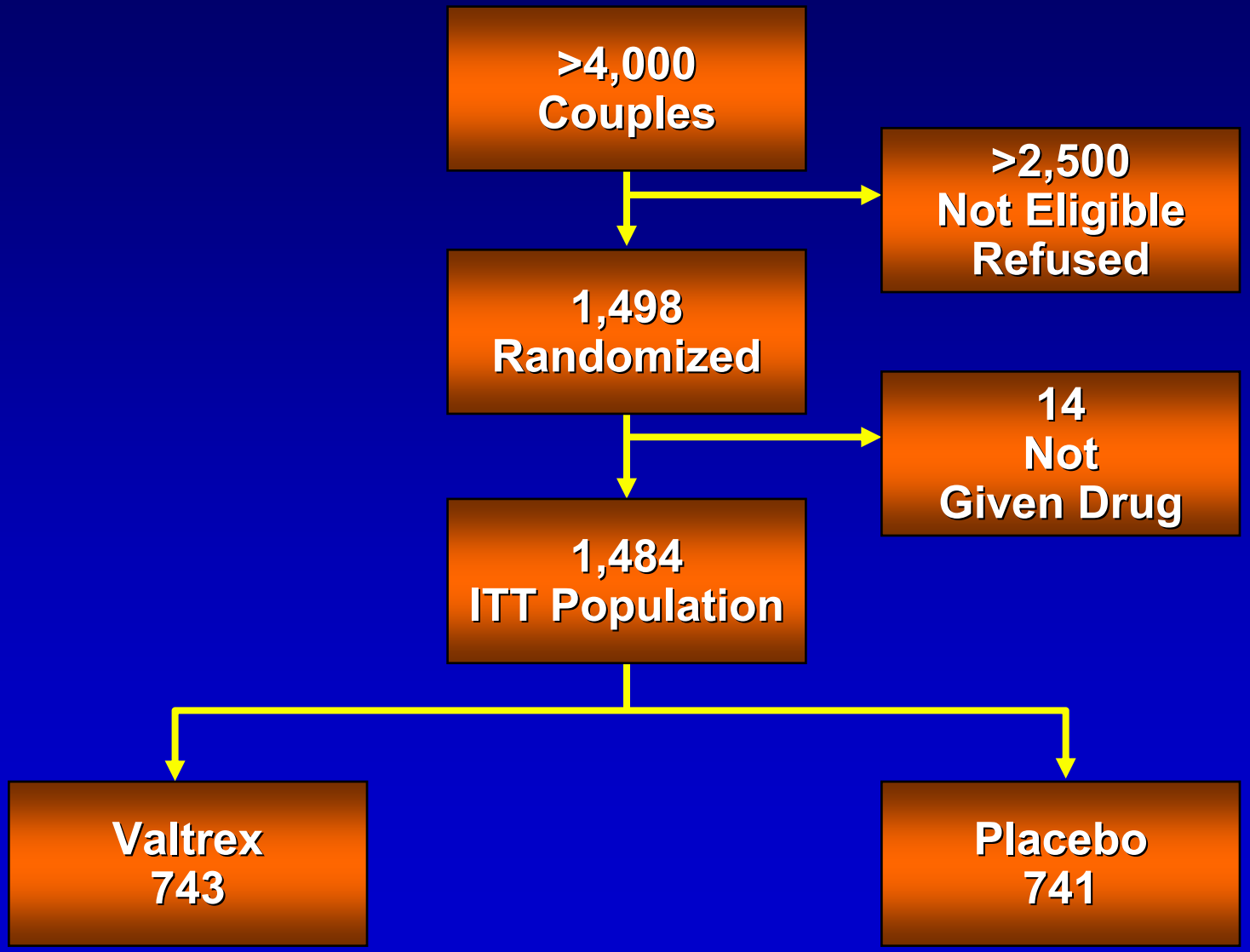
Results

- Description of Study Couples
- Primary Endpoint
- Secondary Endpoints

Couples: Disposition



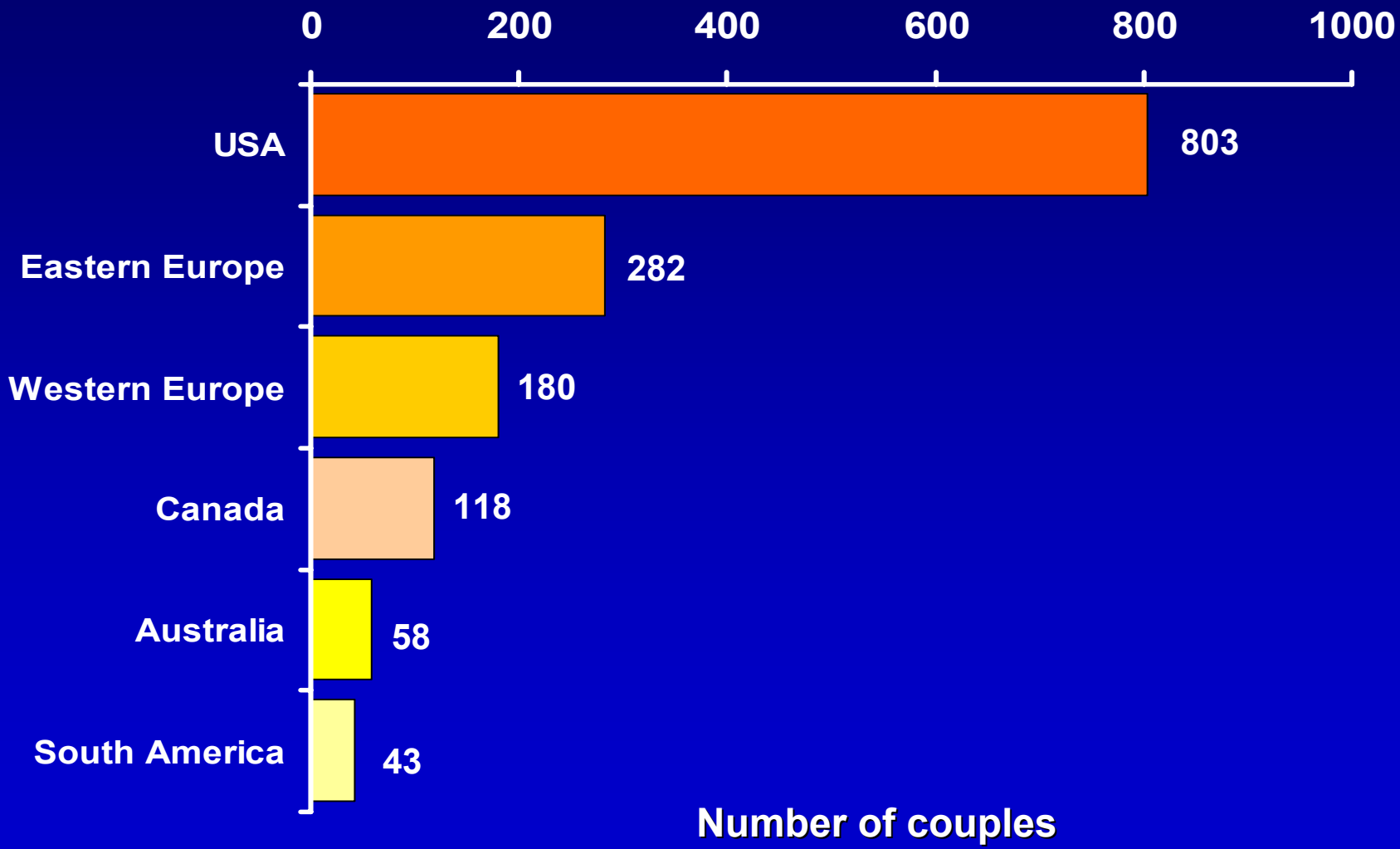
Accountability

- 78% couples completed study
- Most common discontinuation reasons were:

	Placebo	Valtrex
consent withdrawn	7%	4%
lost to follow up	5%	5%
relationship dissolution	4%	4%
other reasons	6%	7%

- Data available from 96% of the ITT population

Recruitment by Region



Demographics

	Placebo (n=741)	Valtrex (n=743)
Male		
Susceptible partners	67%	67%
Source partners	33%	33%
HSV-1 positive at screen		
Susceptible partners	68%	69%
Source partners	54%	51%

Demographics

	Placebo (n=741)	Valtrex (n=743)
Median age, years (range)		
Susceptible partners	34 (18-76)	35 (18-74)
Source partners	34 (19-65)	35 (18-75)
Race - white		
Susceptible partners	90%	89%
Source partners	91%	90%

Baseline Characteristics

	Placebo (n=741)	Valtrex (n=743)
Median recurrences in last year	5	5
Median duration of infection, years	7	7
Median years in relationship	2	2
Median # sex acts in last month	6	7
History of condom use:		
Nearly Always (>90%)	32%	32%
Sometimes (1-90%)	19%	18%
Never	49%	51%

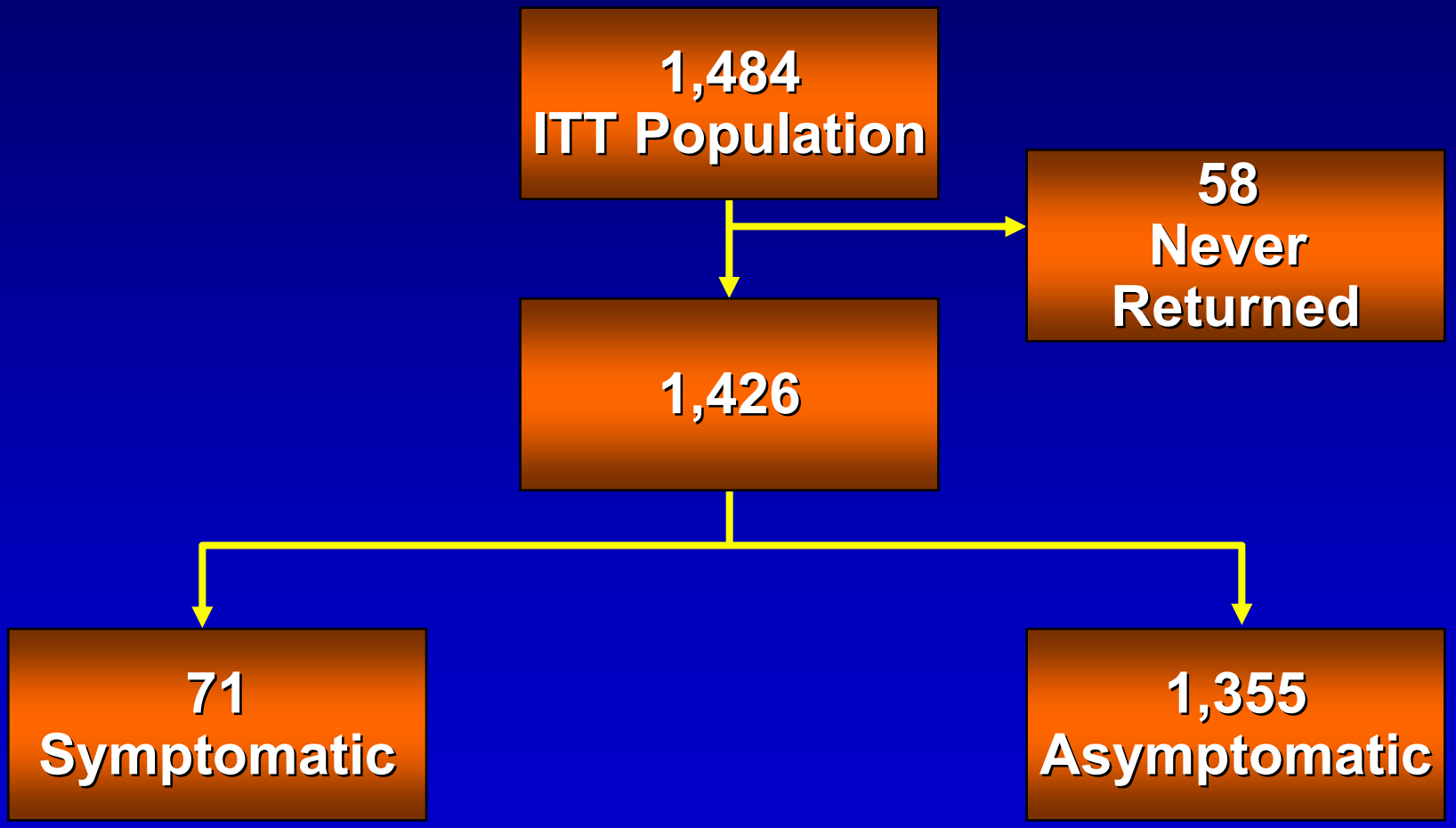
Results

- Description of Study Couples
- **Primary Endpoint**
- Secondary Endpoints

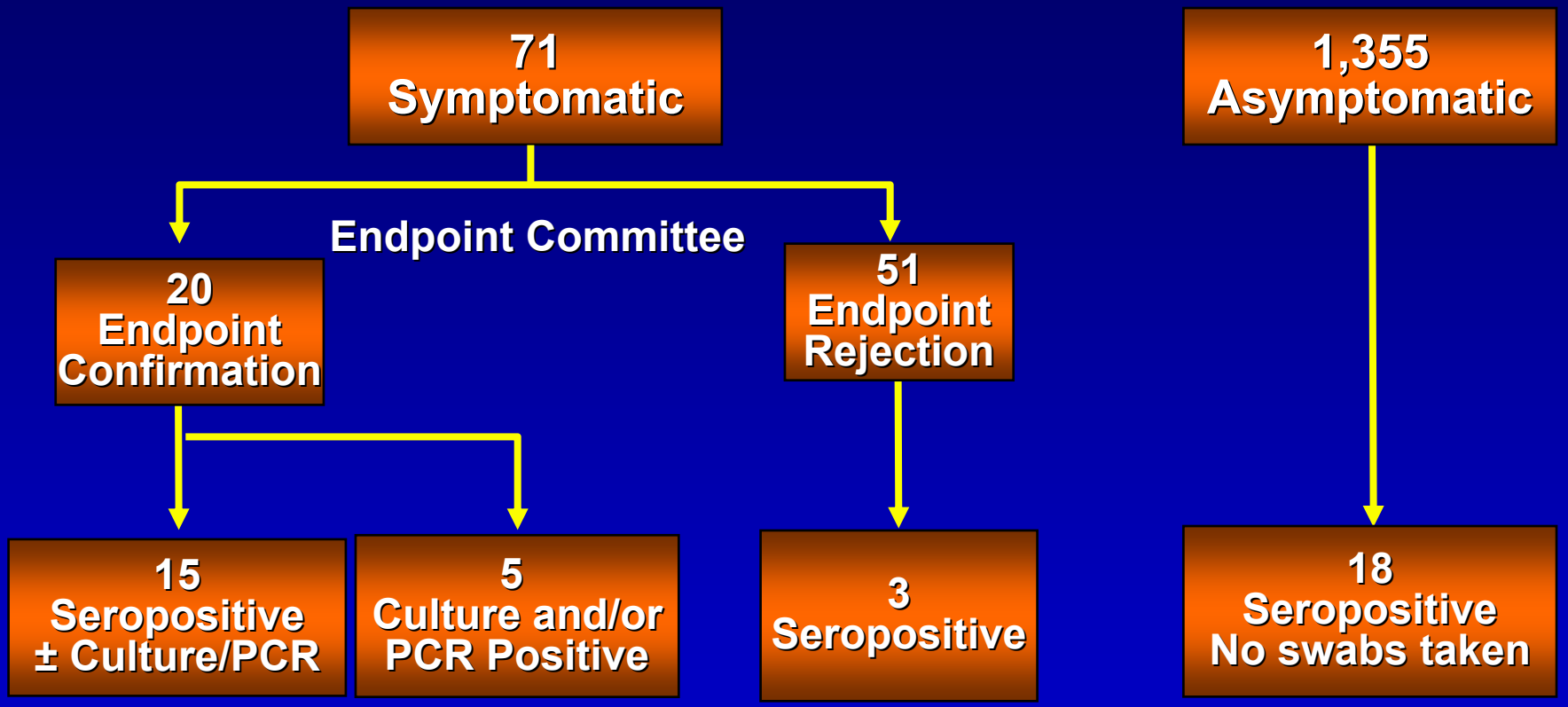
Results

- Description of Study Couples
- **Primary Endpoint**
  - **Endpoint Committee Evaluations**
  - **Proportion of Acquisitions**
  - **Time to Acquisition**
  - **Subanalyses**
- Secondary Endpoints

Endpoint Evaluations

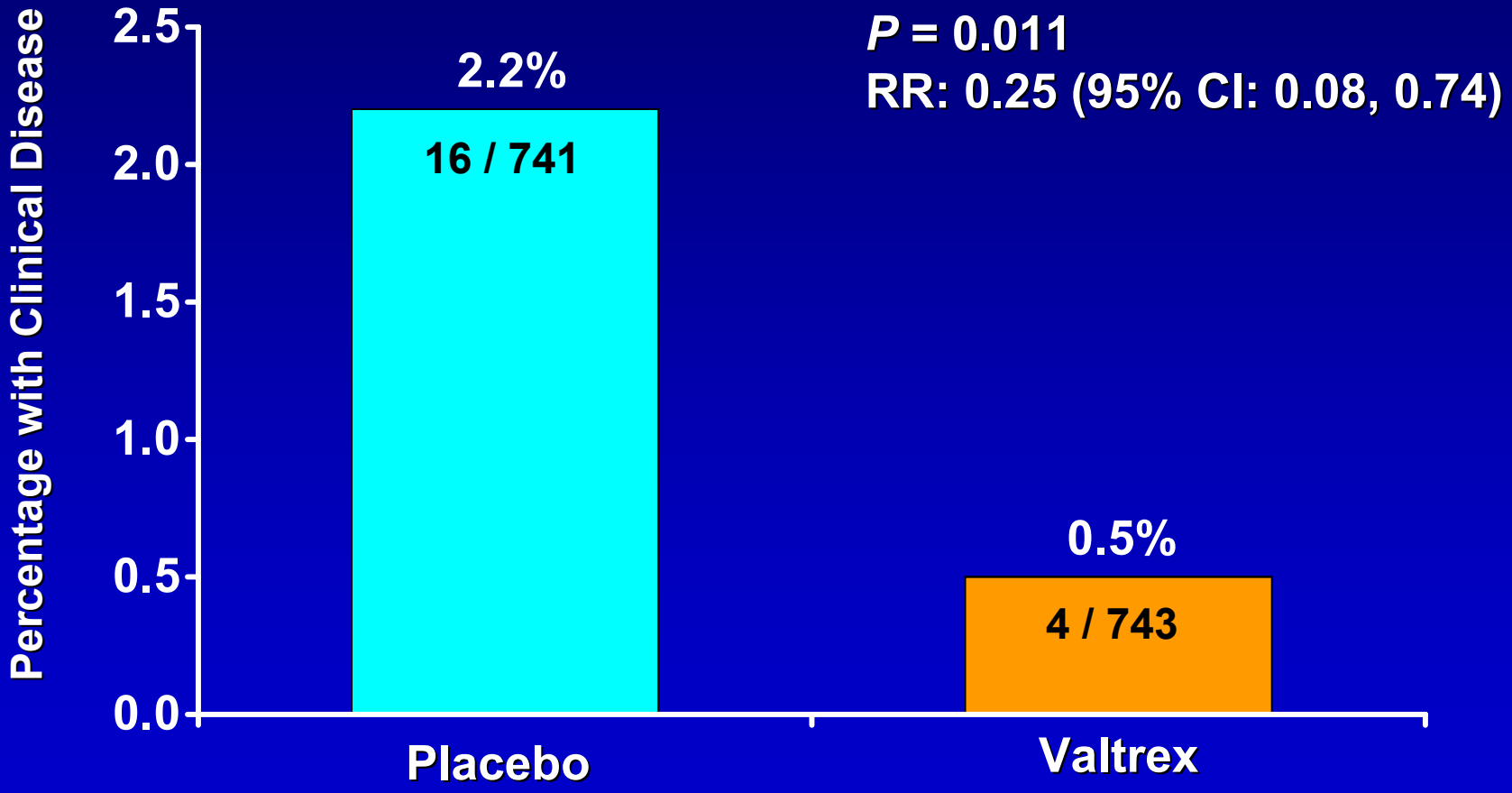


Endpoint Evaluations

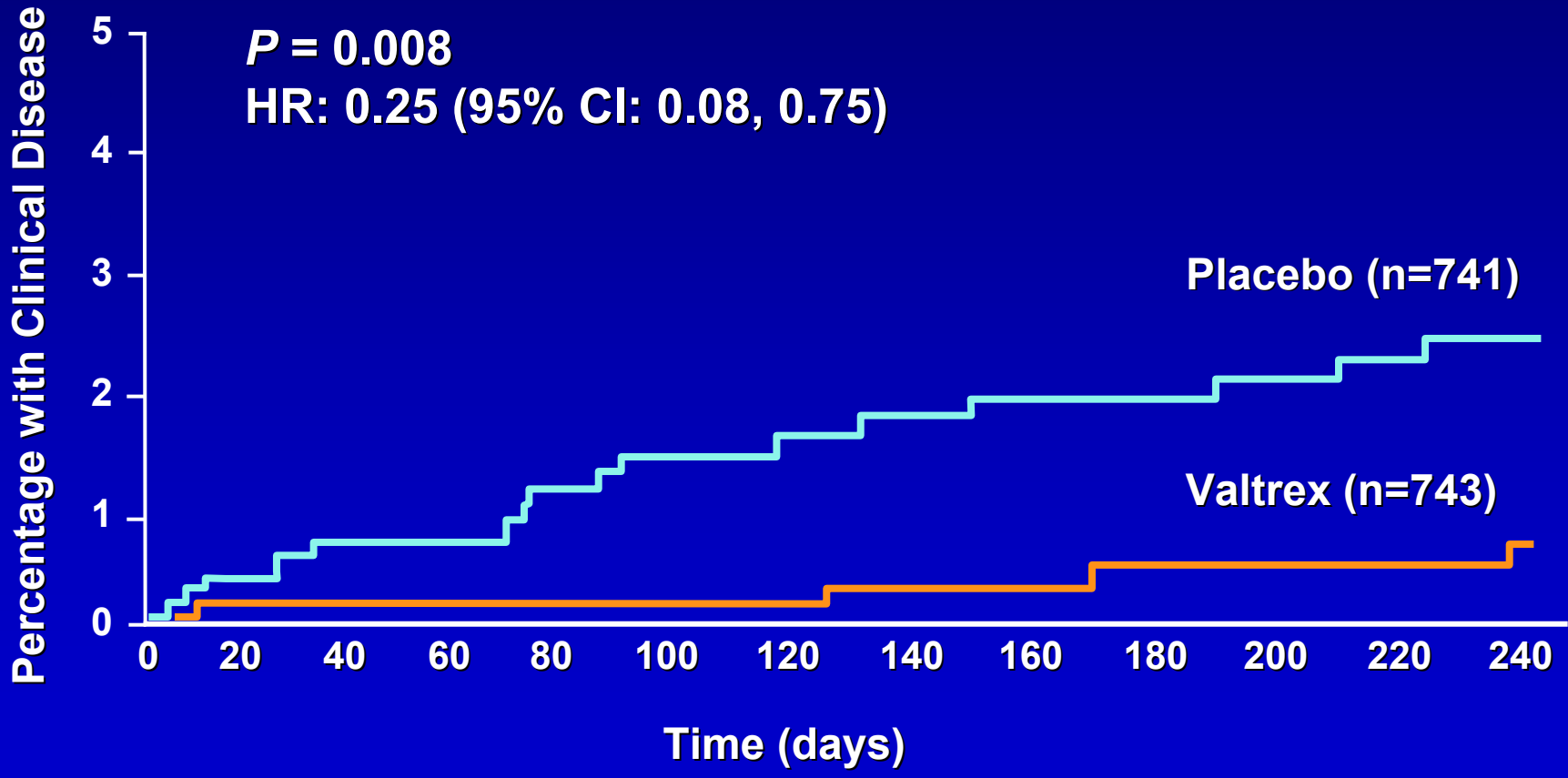


Summary: 20 Confirmed 1^0 Endpoints
36 Seroconversions
41 Overall Acquisitions

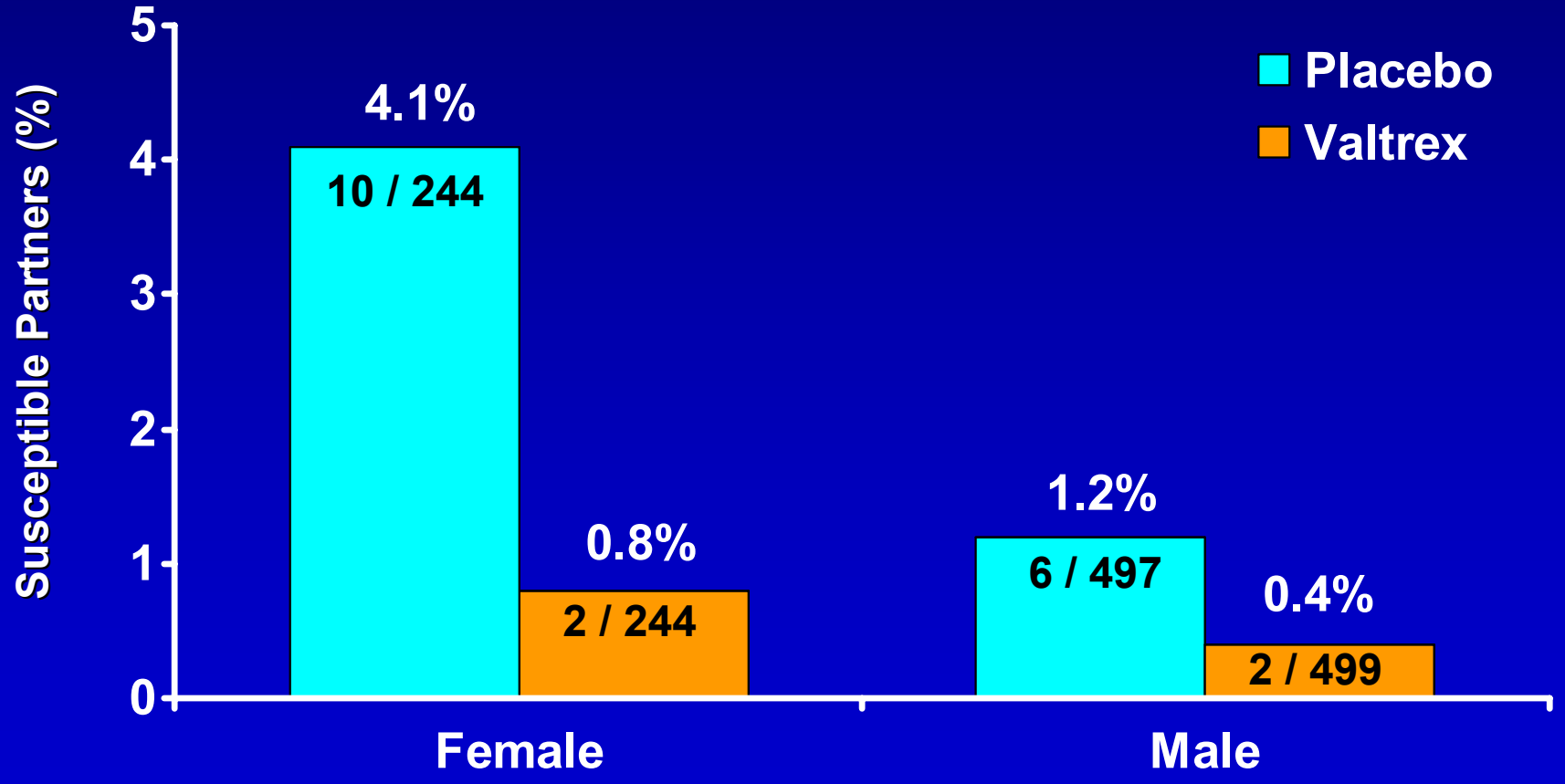
Proportion of Couples with Symptomatic Genital Herpes in Susceptible Partners



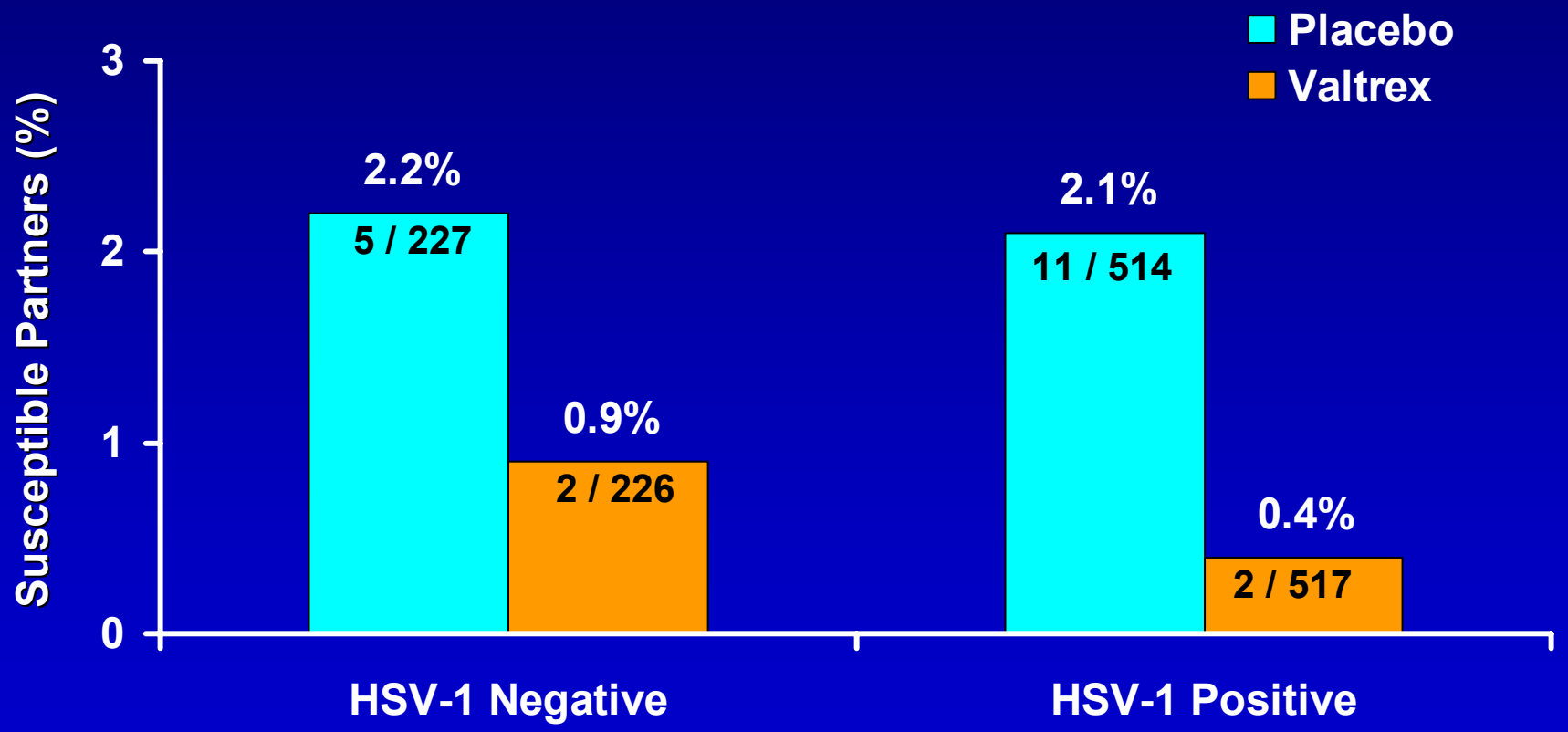
Time to Symptomatic Genital Herpes in Susceptible Partners



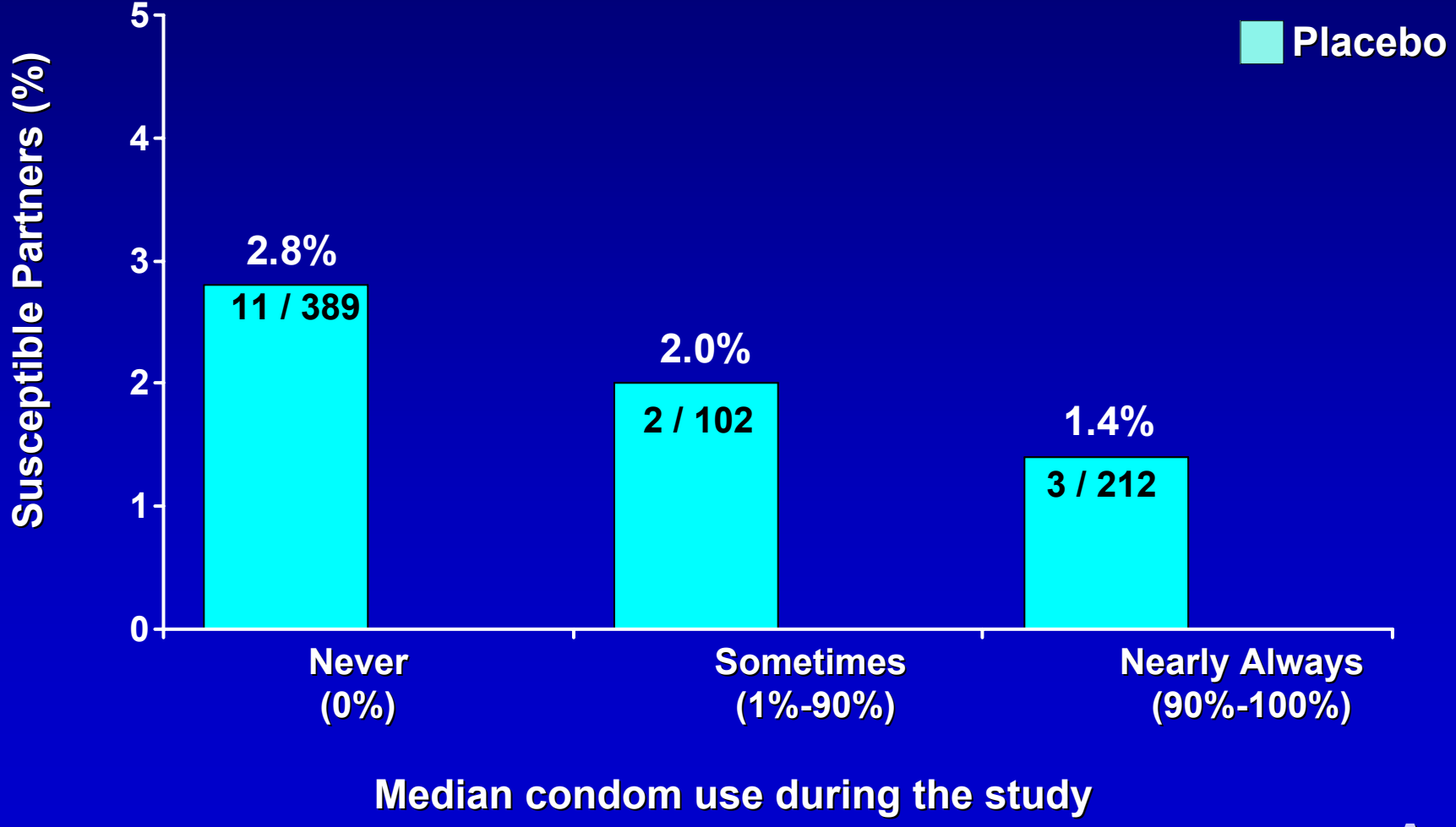
Symptomatic Genital Herpes by Gender of Susceptible Partner



Symptomatic Genital Herpes by HSV-1 Serostatus of Susceptible Partner



Symptomatic Genital Herpes by Condom Use



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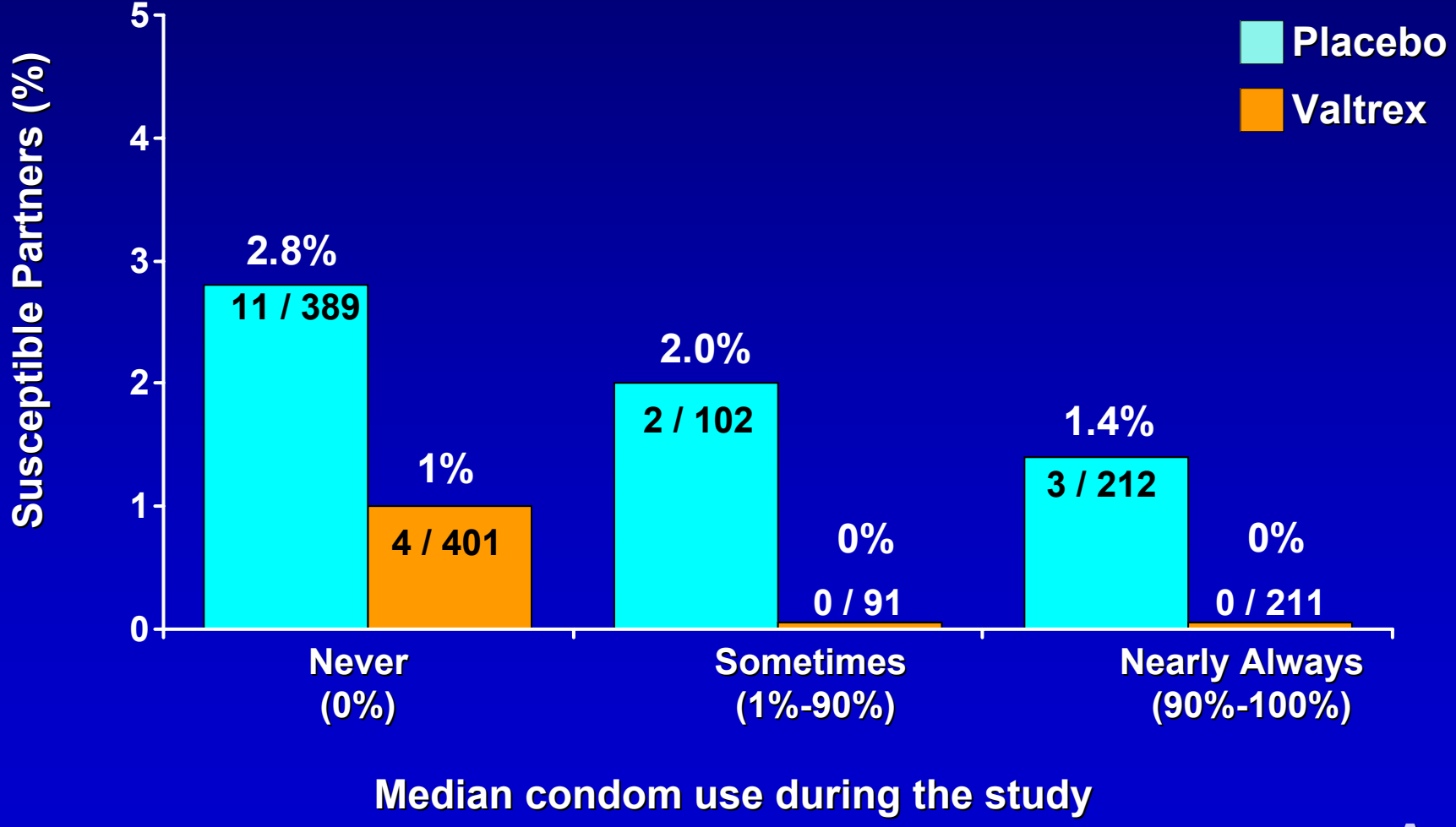


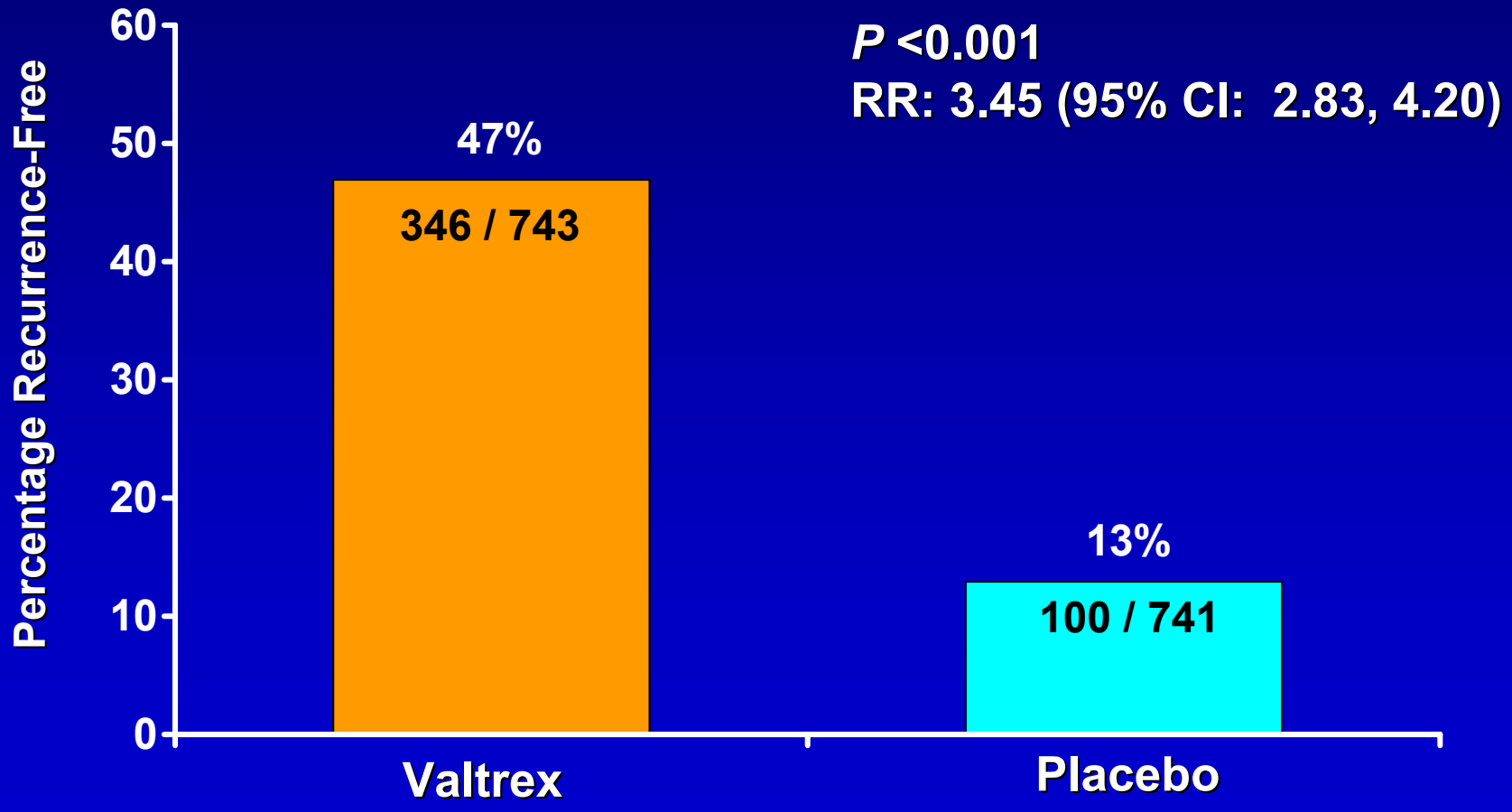
Results

- Description of Study Couples
- Primary Endpoint
- **Secondary Endpoints**

Results

- Description of Study Couples
- Primary Endpoint
- **Secondary Endpoints**
  - **Recurrences in Source Partner**
  - **Viral Shedding**
  - **Overall Acquisitions**

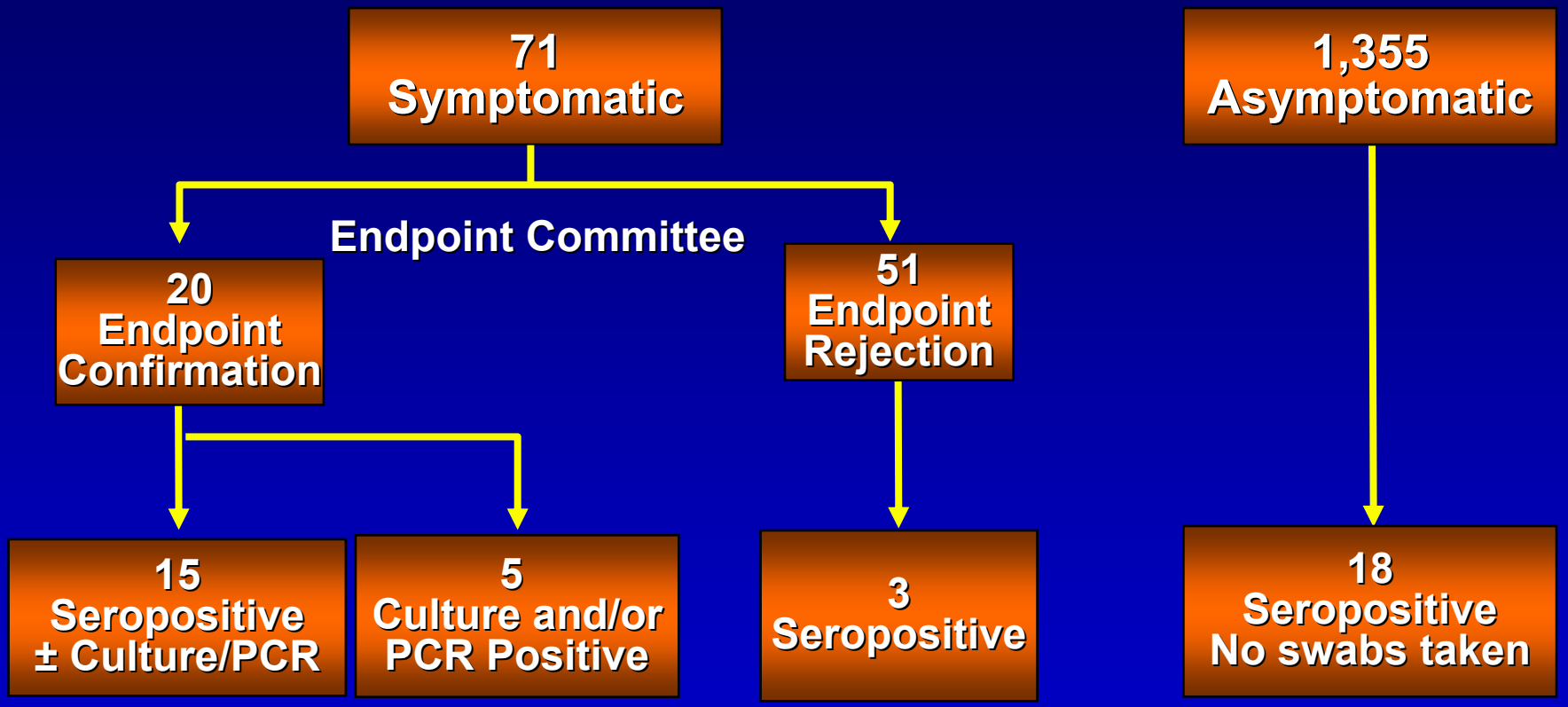
Proportion of Source Partners Recurrence-Free at 8 Months



Viral Shedding by PCR

	Placebo (n=50)	Valtrex (n=39)	P Value
Subjects shedding on 1 or more days	82%	49%	0.002
% of days with shedding (mean)	10.8%	2.9%	<0.001
HSV DNA copies/mL on all days (mean $\log_{10}$)	4.2	1.7	<0.001

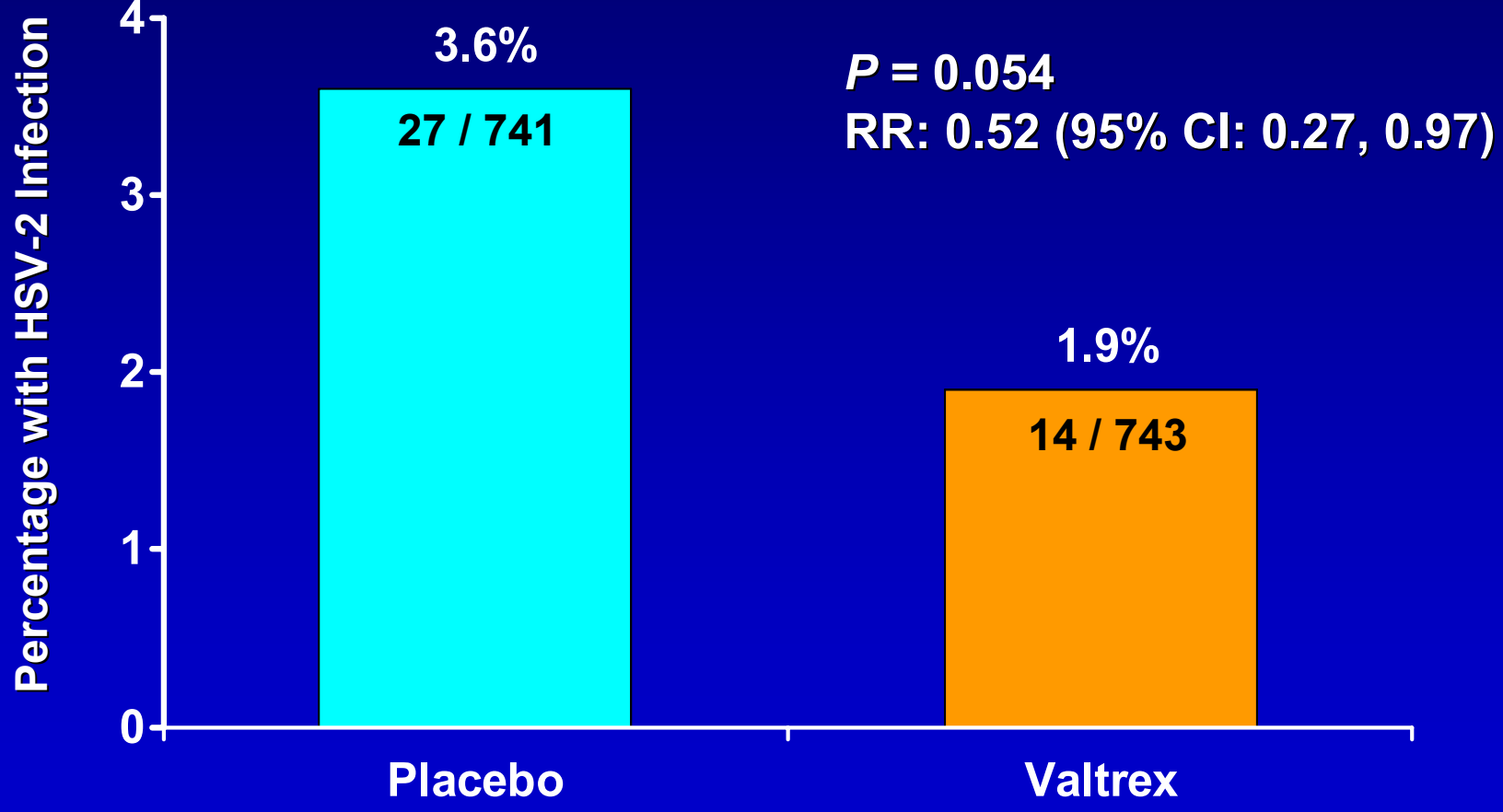
Endpoint Evaluations



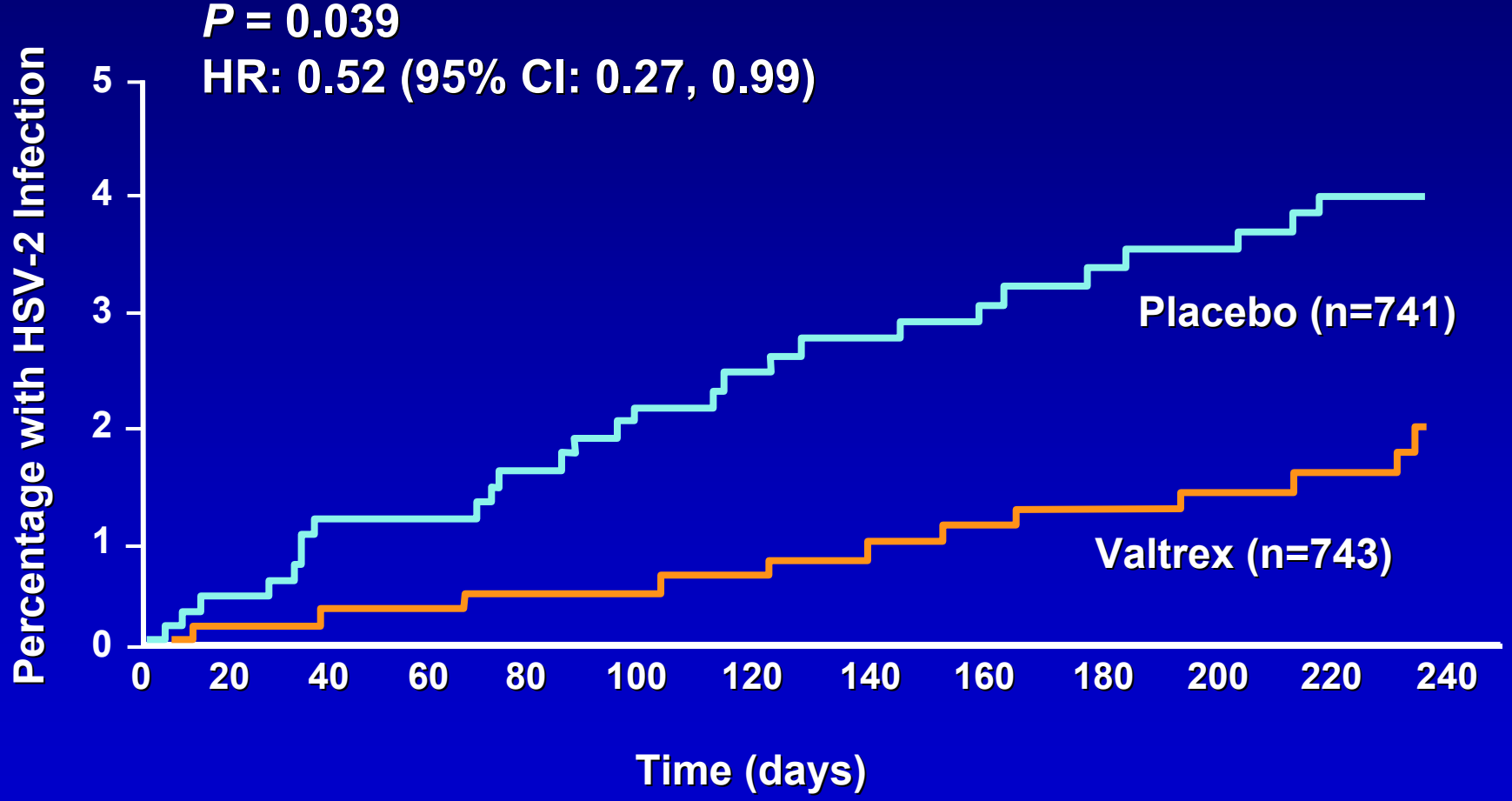
Summary: 20 Confirmed 1^0 Endpoints

41 Overall Acquisitions

Proportion of Susceptible Partners with Overall Acquisition of HSV-2 Infection



Time to Overall Acquisition of HSV-2 Infection in Susceptible Partners



Scope of Presentation

- Rationale
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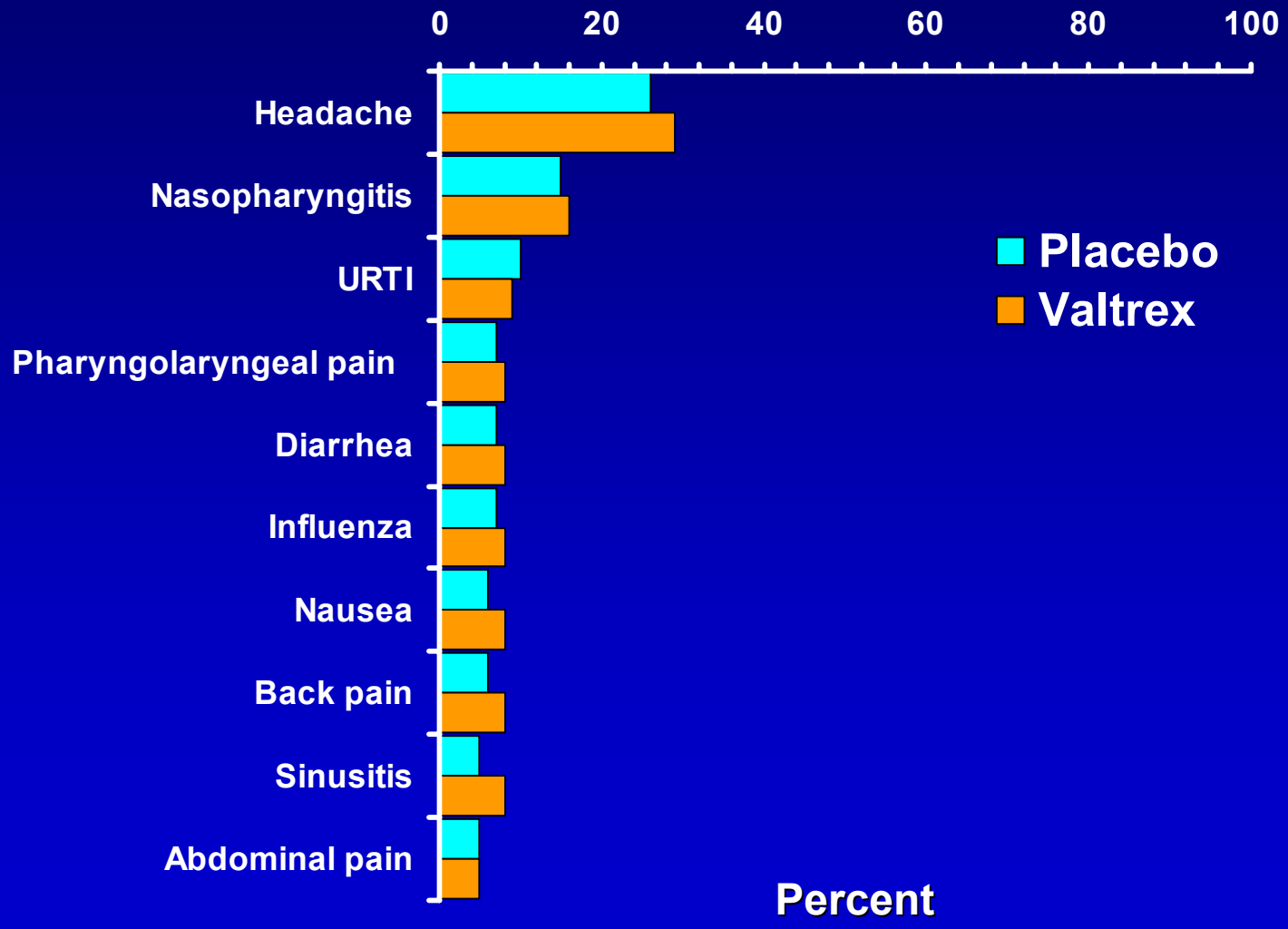
- **Safety**
- Conclusions

Summary of Adverse Events Source Partner: Double-Blind Phase

	Placebo (n=741)	Valtrex (n=743)
Any adverse event	75%	79%
Drug-related adverse event	9%	11%
Serious adverse event	2%	2%
AE leading to treatment d/c	<1%	2%
Deaths	0%	0%

Most Common Adverse Events Source Partner: Double-Blind Phase



Clinically Significant Laboratory Abnormalities
Source Partner: Double-Blind Phase

	Placebo (n=741)	Valtrex (n=743)
Alk. phosphatase (>1.5 x ULN)	0 (0%)	0 (0%)
ALT (>2 x ULN)	16 (2%)	11 (1%)
Creatinine (>1.5 x ULN)	0 (0%)	0 (0%)
Hemoglobin (<0.8 x LLN)	3 (<1%)	5 (<1%)
Platelets (<100,000/mm^3)	0 (0%)	1 (<1%)
WBCs (<0.75 x LLN)	13 (2%)	8 (1%)

Summary of Adverse Events Source Partner: Open-Label Follow-up Phase

- 831 Source Partners
- 68% experienced an adverse event
- Most common:
  - Headache 16%
  - Nasopharyngitis 13%
- 3% serious adverse events
- <1% adverse events leading to withdrawals
- No deaths

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Conclusions

- Study HS2AB3009 met its objectives
- 75% reduction in transmission of clinical infection and 48% overall
- Benefit additional to safer sex counseling and use of condoms
- Well-characterized safety profile

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Valtrex For Prevention Of Genital Herpes Transmission: Implications For Patients And Healthcare Providers

Clarence L. Young, M.D.

Vice President, Anti-Infectives

Clinical Development & Medical Affairs

GlaxoSmithKline

Implications for Patients and Healthcare Providers

- Landmark Study
- New Option for Patient Management
- Communication Plan
- Benefits of Prescribing Information
- Overall Conclusions

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Acknowledgements

- Couples who participated in the study
- Clinical investigators and research personnel
- Some clinical investigators who are here today:
  - Larry Corey, MD, Univ of Washington
  - Zane Brown, MD, Univ of Washington
  - Rhoda Ashley Morrow, PhD, Univ of Washington
  - Larry Stanberry, MD, PhD, Univ of Texas, Galveston
  - Anna Wald, MD, MPH, Univ of Washington
  - Terri Warren, ANP, Westover Heights Clinic, Portland, OR

Subject # 7753
Source Treatment: Valtrex

- Country: USA
- Randomization Date: October 22, 1999
- Date of onset clinical endpoint: June 9, 2000
- Signs and symptoms: Subject reported dysuria approximately four days before noticing a large erythematous papule on her external labia on June 13, 2000. On exam four additional erythematous lesions were identified.
- Confirmatory Labs: Culture taken on June 15, 2000 was positive.

Subject # 7961
Source Treatment: Valtrex

- Country: USA
- Randomization Date: May 6, 1998
- Date of onset clinical endpoint: August 31, 1998
- Signs and symptoms: Subject returned to the clinic on September 2, 1998 with a suspected genital herpes outbreak. Subject stated that prodromal symptoms started on August 31, 1998, with lesions appearing on September 2, 1998. Symptoms reported at the September 2, 1998 office visit included tender, palpable lymph nodes in the bilateral groin, fatigue/malaise, and genital rash.
- Confirmatory Labs: Culture and PCR taken on September 2, 1998 were negative, but serology became atypical on October 13, 1998, then positive on December 2, 1998.

Subject # 8625
Source Treatment: Valtrex

- Country: USA
- Randomization Date: June 22, 1998
- Date of onset clinical endpoint: December 2, 1998
- Signs and symptoms: Subject returned to the clinic on December 2, 1998 with complaints of sore throat, genital tenderness, and genital lesion that started on December 2.
- Confirmatory Labs: Both culture and PCR from December 2, 1998 visit were positive.

Subject # 10987
Source Treatment: Valtrex

- Country: USA
- Randomization Date: April 21, 1998
- Date of onset clinical endpoint: April 29, 1998
- Signs and symptoms: Subject presented to the clinic on May 1, 1998 complaining of dysuria lasting 2 days. On exam, the labia was erythematous with no discrete lesions and extensive cervicitis.
- Confirmatory Labs: Culture and PCR from the May 1, 1998 visit were positive. In addition, serology from the May 20, 1998 visit (month 1 of episode) was positive.

Summary of Missing Data for Primary Endpoint (ITT)

	Placebo (n = 741)	Valtrex (n = 743)
Susceptible partners who discontinued before completing the 8 month double-blind study	163 (22%)	158 (21%)
Time followed for primary endpoint prior to discontinuation:		
< 3 months	90 (55%)	85 (54%)
3 to < 6 months	55 (34%)	52 (33%)
≥ 6 months	18 (11%)	21 (13%)

Sensitivity Analyses for the Prospectively Defined Primary Endpoint

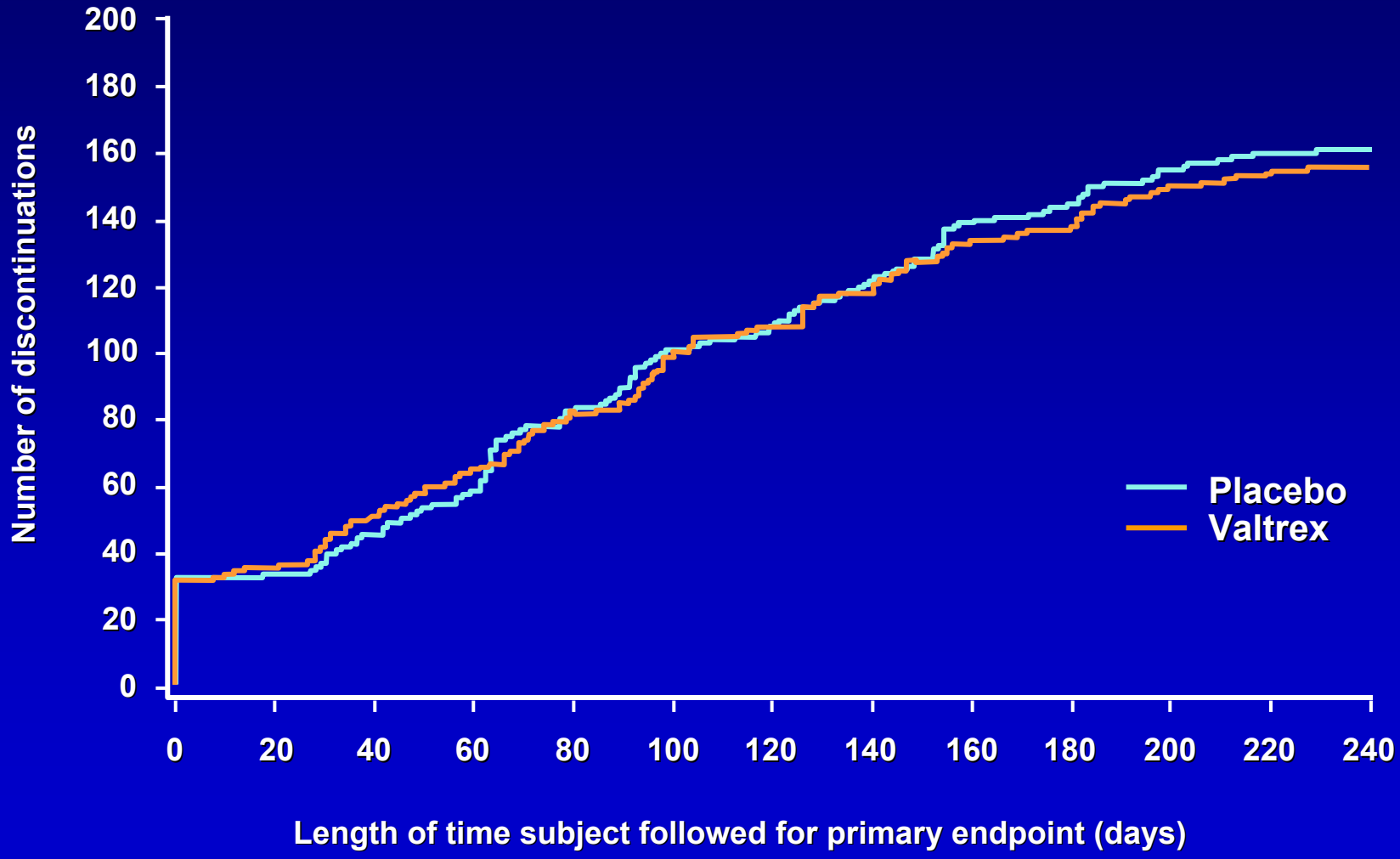
Key sensitivity analyses were provided to FDA:

- Time-to-Event Analysis: uses all data for a susceptible partner up to the time of discontinuation
- As Treated Analysis: analysis excludes susceptible partners who discontinued
- Imputation Approach: endpoints imputed at the placebo rate for both treatment groups

All 3 methods show superiority of Valtrex over placebo

Figure 3

Susceptible Partner Discontinuations: Length of Time Followed for Primary Endpoint



Summary of Key Sensitivity Analyses for Primary Endpoint

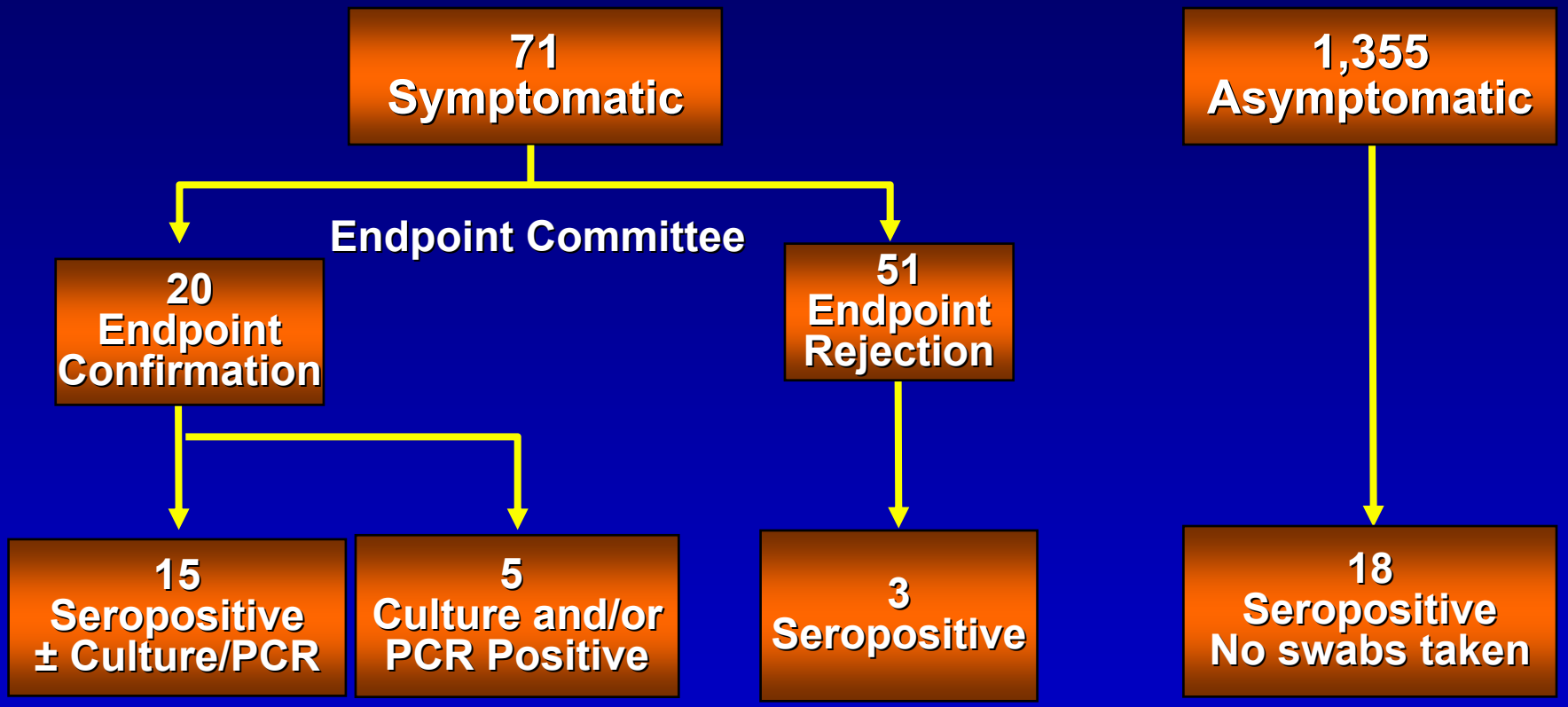
Analysis	Point Estimate	95% confidence limit	p-value
Primary	Odds Ratio = 0.24	(0.06, 0.76)	0.011
Time-to-event	Hazard Ratio = 0.25	(0.08, 0.75)	0.008
As treated	Odds Ratio = 0.25	(0.06, 0.77)	0.012
Placebo rate imputation: 4 events added 5 events added	 Odds Ratio = 0.39 Odds Ratio = 0.42	 (0.15, 0.94) (0.17, 0.96)	 0.033 0.040

Potential Discontinuation Bias Based On Various Factors

Potential Predictive Factor	Predictive for Discontinuation	Predictive for Primary Outcome	Differential Discontinuation by Treatment
Gender	No	----	----
HSV-1 for source	No	----	----
Age for source	No	----	----
Age for susceptible	No	----	----
Recurrence history (source)	No	----	----
HSV-1 for susceptible	Yes	No	----
Country (US, Non-US)	Yes	Yes	No
Duration of relationship	Yes	Yes	No
Duration of HSV-2 (source)	Yes	Yes	Yes*

*Implies a potential bias against Valtrex because shorter duration of HSV-2 infection is correlated with clinical acquisition, and is also associated with a higher discontinuation rate for placebo.

Endpoint Evaluations



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Summary by Compliance of Symptomatic Genital HSV-2 Infection in Susceptible Partners

	Placebo (n=16)	Valtrex (n=4)
<80%	0	0
80-<85%	1	1
85-<90%	0	0
90-<95%	2	0
>=95%	13	3

Subjects with missing information for number of tablets returned were considered compliant
Subjects with any other missing information were considered non-compliant

Summary by Compliance of Overall Acquisition of Genital HSV-2 Infection in Susceptible Partners

	Placebo (n=27)	Valtrex (n=14)
<80%	0	1
80-<85%	1	1
85-<90%	1	2
90-<95%	2	4
>=95%	23	6

Subjects with missing information for number of tablets returned will be considered compliant
Subjects with any other missing information will be considered non-compliant

Summary of Treatment Compliance in Double Blind Phase

	Placebo (n=741)		Valtrex (n=743)		Total (n=1484)	
n	741		743		1484	
0%*	41	(6%)	40	(5%)	81	(5%)
<40%	0	(0%)	1	(<1%)	1	(<1%)
40%-<60%	5	(<1%)	1	(<1%)	6	(<1%)
60%-<80%	22	(3%)	10	(1%)	32	(2%)
>=80%	673	(91%)	691	(93%)	1364	(92%)

Subject with missing information for number of caplets returned were considered fully compliant

*Subjects with any other missing information were considered non-compliant

Condom use reported by susceptible partners at baseline and during the study

	Valacyclovir (N=743)	Placebo (N=741)
Condom use at baseline Never "Nearly Always"	368/725 (51%) 229/725 (32%)	352/713 (49%) 226/713 (32%)
Condom use for vaginal sex during the study Never "Nearly Always"	400/703 (57%) 211/703 (30%)	388/703 (55%) 212/703 (30%)
Condom use for oral sex during the study Never "Nearly Always"	478/556 (86%) 38/556 (7%)	477/537 (89%) 39/537 (7%)

"Nearly Always" = 90-100% - Median usage over months 1-8.