

**In a Randomized Phase II Trial
Casopitant Mesylate + Ondansetron
and Dexamethasone Reduced
Chemotherapy-Induced
Nausea/Vomiting (CINV) in Patients
Receiving Moderately Emetogenic
Chemotherapy (MEC)**

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Background

- A combination of a 5-HT₃ receptor antagonist (RA) plus a corticosteroid is a standard of care for the prevention of CINV due to MEC although the effect on delayed CINV has been disappointing
- Neurokinin-1 (NK-1) RAs suppress the activity of the nucleus tractus solitarius (NTS) and antagonize the effects of the neurotransmitter substance P
- Triple therapy that includes an NK-1 RA has been shown to improve the control of MEC-induced CINV (Warr et al. *J Clin Oncol.* 2005)
- Triple therapy with casopitant mesylate, a potent, selective NK-1 RA, was evaluated in this multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group study

NKV101983 Study Design

Multicenter, randomized, double-blind, placebo-controlled,
dose-ranging, parallel group study

Arm	Day 1	Day 2	Day 3
1	Ondansetron 8 mg bid Dex 8 mg IV	Ondansetron 8 mg bid PO	Ondansetron 8 mg bid PO
2	Ondansetron 8 mg bid Dex 8 mg IV Casopitant 50 mg PO	Ondansetron 8 mg bid PO Casopitant 50 mg PO	Ondansetron 8 mg bid PO Casopitant 50 mg PO
3	Ondansetron 8 mg bid Dex 8 mg IV Casopitant 100 mg PO	Ondansetron 8 mg bid PO Casopitant 100 mg PO	Ondansetron 8 mg bid PO Casopitant 100 mg PO
4	Ondansetron 8 mg bid Dex 8 mg IV Casopitant 150 mg PO	Ondansetron 8 mg bid PO Casopitant 150 mg PO	Ondansetron 8 mg bid PO Casopitant 150 mg PO
5	Ondansetron 8 mg bid Dex 8 mg IV Casopitant 150 mg PO	Ondansetron 8 mg bid PO	Ondansetron 8 mg bid PO
6	Ondansetron 16 mg Dex 8 mg IV Casopitant 150 mg PO	Ondansetron 16 mg qd PO Casopitant 150 mg PO	Ondansetron 16 mg qd PO Casopitant 150 mg PO

R

Exploratory arms

Study Endpoints

- **Primary**

- The proportion of patients who achieve a complete response (CR: defined as no vomiting, no retching, no rescue medications and no premature withdrawals) during the first 120 hour evaluation period from the initiation of MEC
- The proportion of patients who have no significant nausea (< 25 mm on the VAS) during the first 120 hour evaluation period from the initiation of MEC

- **Secondary**

- No nausea (VAS < 5 mm)
- Time to emesis and rescue
- Impact on daily life activities as measured by the Functional Living Index-Emesis (FLIE)
- Safety
- Population pharmacokinetics

Key Eligibility Criteria

- **Inclusion**

- Patients with solid tumors scheduled to receive their first course of MEC
- Karnofsky Performance Status ≥ 70

- **Exclusion**

- History of prior chemotherapy
- Known CNS primary or metastatic disease
- Initiated systemic corticosteroid therapy within 72 hours of the first dose of study drug (taxane prophylaxis permitted)
- Use of any other medication with antiemetic potential within 24 hours of a dose of study drug
- Concurrent use of potential inducers or inhibitors of CYP3A4 or CYP3A5
- Adjuvant cyclophosphamide-containing regimens

Eligible MEC Regimens

- **Cyclophosphamide as follows:**
 - Total dose within a dose range of 500–1500 mg/m² if combined with other chemotherapeutics of moderate emetogenic potential
 - Total dose within a dose range of 750–1500 mg/m² if administered as monotherapy or with other chemotherapeutics of minimal or low emetogenic potential.
 - Total infusion time not to exceed two (2) hours
- **Platinum**
 - Carboplatin, AUC (area under the curve) ≥ 5
 - Oxaliplatin ≥ 85 mg/m²; total infusion time not to exceed 2 hours
- **Anthracycline**
 - Doxorubicin ≥ 60 mg/m²; total infusion time not to exceed 1 hour
 - Epirubicin ≥ 90 mg/m²

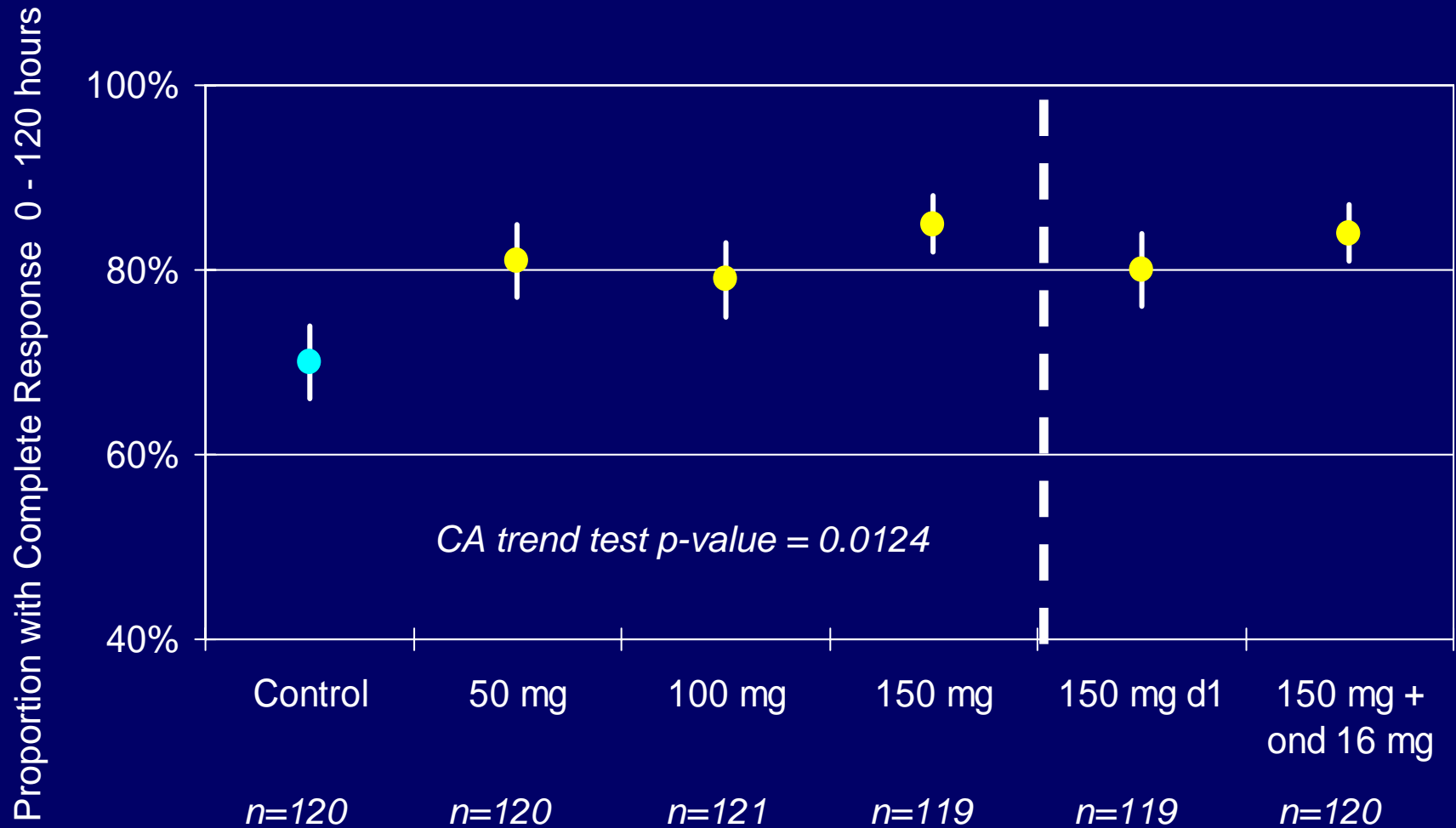
Patient Demographics

Total N (ITT) = 719

	Control	Casopitant				
		50mg	100mg	150mg	150mg + D1	150mg + Ond 16mg
N*	119	119	121	116	117	119
Age						
Mean (SD)	57 (11.9)	59 (11.8)	57 (12.7)	59 (12.1)	58 (13.0)	58 (12.9)
Median	57	58	58	60	58	59
Gender						
Female	62%	62%	60%	60%	60%	60%
Male	38%	38%	40%	40%	40%	40%

* Age-related data not available for entire ITT population

Complete Response (120 hrs)* (ITT)



* Treatments to the right of the line are not included in the primary analysis.

Complete Response Rates (ITT)

	Control	Casopitant		
		50 mg	100 mg	150 mg
CR (0 – 120h)	70%	81%	79%	85%
C-A trend test p-value	0.0124			
p-value*		0.0410	0.1092	0.0124
CR (0 – 24h)	90%	92%	89%	92%
C-A trend test p-value	0.6721			
p-value*		0.6536	0.8329	0.6721
CR (24 – 120h)	70%	81%	79%	85%
C-A trend test p-value	0.0124			
p-value*		0.0410	0.1092	0.0124

Casopitant	
150 mg D 1 [†]	150 mg + Ond 16 mg [†]
80%	84%

91%	93%
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80%	84%
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*p-value for ordinal contrast, not pairwise comparison

[†]Exploratory arms not included in primary analysis

Complete Response By Stratification Factors (ITT)

	Control	Casopitant		
		50mg	100mg	150mg
CR (0 – 120h)	70%	81%	79%	85%
C-A trend test p-value	0.0124			
p-value*		0.0410	0.1092	0.0124

Casopitant	
150 mg D 1 [†]	150 mg + Ond 16 mg [†]
80%	84%

CR (0 – 120h)

Taxane N=246	73%	85%	80%	85%
Non-taxane N=473	68%	78%	78%	85%

80%	90%
79%	81%

Female N=431	68%	79%	73%	86%
Male N=280	72%	83%	88%	83%

77%	85%
83%	83%

AC Regimen** N=115	69%	80%	83%	88%
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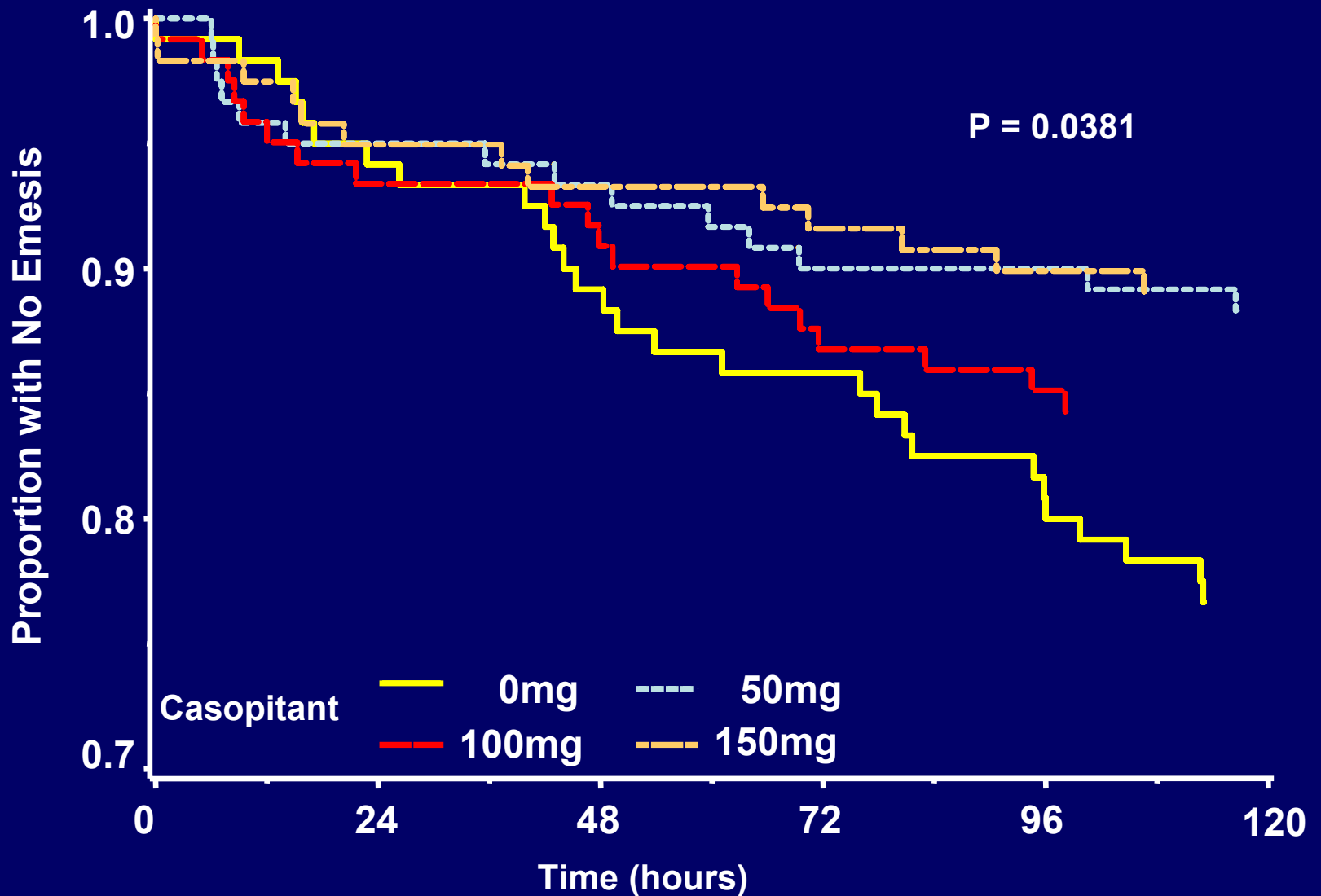
84%	85%
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* = p-value for ordinal contrast, not pairwise comparison

** = not prospectively stratified

[†]Exploratory arms not included in primary analysis

Time to Emesis (ITT)



No Vomiting (ITT)

	Control	Casopitant		
		50mg	100mg	150mg
No vomiting (0 – 120h)	77%	88%	84%	89%
CA test p-value	0.0257			
p-value*		0.0124	0.1037	0.0257
No vomiting (0 – 24h)	94%	95%	93%	95%
CA test p-value	0.9268			
No vomiting (24 – 120h)	78%	90%	88%	92%
CA test p-value	0.0072			
p-value*		0.0075	0.0340	0.0072

Casopitant	
150 mg D 1 [†]	150 mg + Ond 16 mg [†]
84%	90%

93%	96%
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88%	93%
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* = p-value for ordinal contrast, not pairwise comparison

[†]Exploratory arms not included in primary analysis

Nausea, Rescue, and Daily Life Activities

- **No significant difference in the rates of 'no significant nausea' and 'no nausea' among groups**
- **No significant difference in the use of rescue medication among groups**
- **No significant difference in daily life activities**

Safety*

	Control	Casopitant				Casopitant 150 mg + Ond 16mg
		50mg	100mg	150mg	150mg D1	
N=	119	119	121	116	117	120
Any event	67%	66%	67%	70%	61%	66%
Nausea	11%	14%	24%	13%	16%	13%
Constipation	12%	12%	12%	9%	12%	12%
Diarrhea	4%	9%	7%	11%	9%	9%
Fatigue	13%	11%	18%	15%	15%	17%
Anemia	13%	9%	9%	10%	8%	10%
Neutropenia	12%	12%	12%	12%	12%	13%
Alopecia	8%	8%	12%	10%	12%	8%
Anorexia	6%	6%	14%	4%	10%	6%

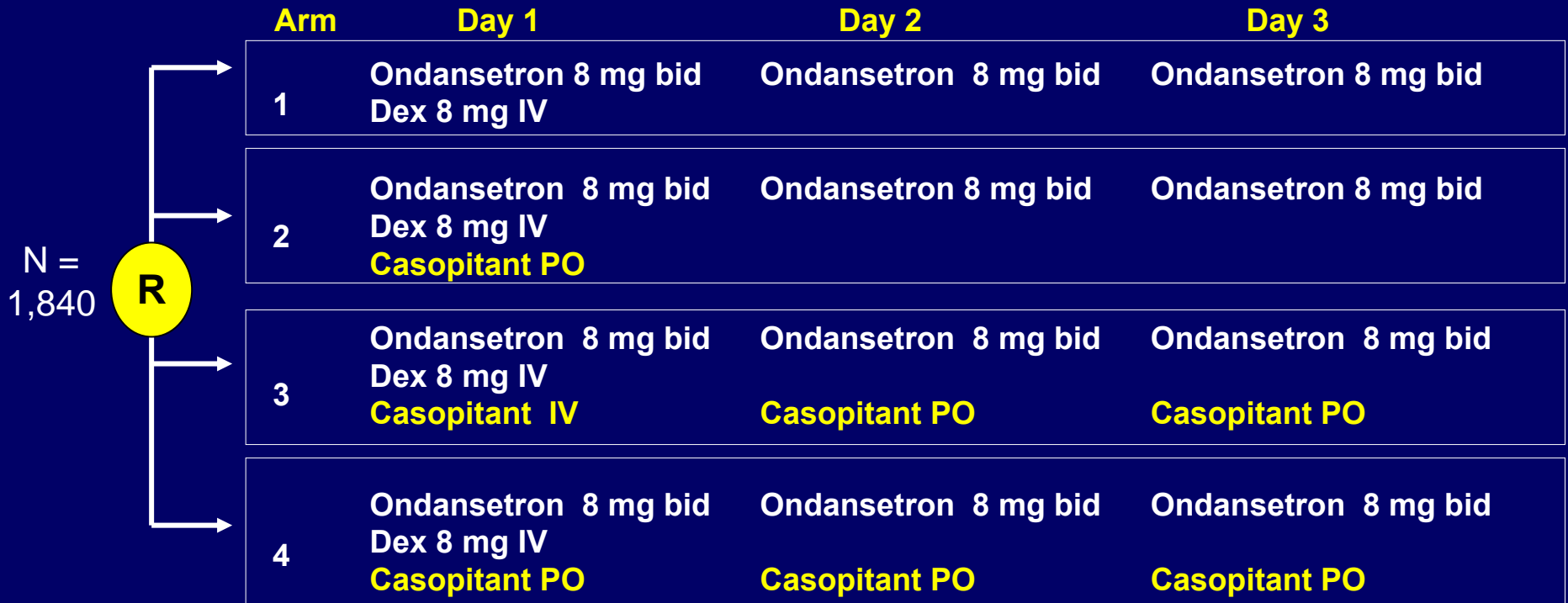
- **Serious adverse events were reported for 75 (11%) patients**
- **Drug-related adverse events were reported in 94 (13%) patients**

*Most common adverse events ($\geq 10\%$, any concentration), regardless of cause, for cycle 1

Conclusions

- **The addition of casopitant to ondansetron-dexamethasone significantly reduced MEC-associated CINV compared to ondansetron-dexamethasone at all dose levels tested as measured by CR**
 - **Overall and delayed CR, 0-120 and 24-120 hrs, CA Trend test p-value =0.0124**
- **There were no significant differences in rates of nausea, significant nausea, rescue medications, or FLIE among groups**
- **All casopitant regimens were generally well tolerated**
- **Activity associated with the 1-day casopitant regimen was encouraging**
- **Phase III studies planned to initiate in second half of 2006**

Phase 3 MEC Study Design: NKV102549



- Multicenter, Randomized, Double-Blind, Active-Control Study
- Objective: Prevention of CINV associated with MEC
- Primary endpoint: Complete response (no vomiting, retching or rescue) at 120 hrs
- Global enrollment expected to initiate 2nd-half of 2006

Dex = dexamethasone