Study Synopsis

1. Proprietary Drug Name: EMEND™	**2. Generic Drug Name:** aprepitant	**3. Therapeutic area and FDA-approved indications:** Moderately emetogenic chemotherapy-induced nausea and vomiting
4. Name of Sponsor/Company:	Merck & Co., Inc., Whitehouse Station, New Jersey, USA	
5. Title of Study:	A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy - Aprepitant MEC Study (AVERT) NCT00092183 (PN 071)	
6. Study Investigators/Study Center(s):	Multicenter (109), multinational	
7. Studied Period (years): Oct-2002 to Apr-2004		**8. Phase of development:** III

9. Primary Hypotheses and Secondary Hypothesis:

Primary Hypotheses

(1) The Aprepitant Regimen will be superior to the Standard Regimen, as measured by the proportion of patients with Complete Response in the 120 hours following the first cycle of chemotherapy; (2) The Aprepitant Regimen and the Standard Regimen will be well tolerated in the first cycle of chemotherapy.

Secondary Hypothesis

The Aprepitant Regimen will be superior to the Standard Regimen, as measured by the proportion of patients with no impact on daily life on the Functional Living Index—Emesis (FLIE) questionnaire in the first cycle of chemotherapy.

10. Study Design/ Methodology:

Multicenter, randomized, double-blind, parallel-group trial with in-house blinding to assess the efficacy and tolerability of aprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV). The protocol had 3 components. The first component focused on the initial cycle of chemotherapy. The second component consisted of an optional multiple-cycle extension for up to 3 subsequent cycles of chemotherapy. The third component consisted of an optional open-label multiple-cycle extension (Cycles 5-7).

11. Number of Patients (planned and analyzed):

PATIENT DISPOSITION:

Overall Disposition of Patients—Cycle 1

Time Frame	Aprepitant Regimen	Standard Regimen	Total
ENTERED: Total Male (age range-years) Female (age range-years)	n=438 2 (55 to 60) 436 (25 to 78)	n=428 0 428 (23 to 78)	N=866 2 (55 to 60) 864 (23 to 78)
SCREENING FAILURES:			44
Patient discontinued prior to completion of Cycle 1; reason provided below:	8	7	15
Clinical AE	2	1	3
Lack efficacy	3	2	5
Pt. discontinued for other reason	1	0	1
Pt. withdrew consent	1	4	5
Protocol deviation	1	0	1
Patient completed Cycle 1 and did not continue; reason provided below:	45	62	107
Clinical AE	5	5	10
Ineligible	3	7	10
Laboratory AE	2	1	3
Lack efficacy	17	31	48
Non-compliance with Rx	0	1	1
Pt. withdrew consent	16	14	30
Protocol deviation	2	2	4
Refused chemotherapy	0	1	1
Patient completed and entered Cycle 2	385	359	744

AE = adverse experience, Pt = patient

Number (%) of Patients in Cycles 2 to 4 by Treatment Group

	Aprepitant Regimen (N=438)	Standard Regimen (N=428)	Total (N=866)
	n (%)	n (%)	n (%)
Cycle 2			
Discontinued During:	4 (0.9%)	4 (0.9%)	8 (0.9%)
Discontinued After:	17 (3.9%)	20 (4.7%)	37 (4.3%)
Continuing:	364 (83.1%)	335 (78.3%)	699 (80.7%)
Cycle 3			
Discontinued During:	4 (0.9%)	9 (2.1%)	13 (1.5%)
Discontinued After:	10 (2.3%)	14 (3.3%)	24 (2.8%)
Continuing:	350 (79.9%)	312 (72.9%)	662 (76.4%)
Cycle 4			
Discontinued During:	9 (2.1%)	3 (0.7%)	12 (1.4%)
Completed:	341 (77.9%)	309 (72.2%)	650 (75.1%)

Overall Disposition of Patients - Cycles 5 to 7 (Open-Label Extension)	
Treatment Cycle	Aprepitant Regimen
Cycle 5	**n=75**
Patient discontinued after completion of Cycle 5; reason provided below:	4
Laboratory adverse experience	1
Patient withdrew consent	2
Protocol deviation	1
Patient completed Cycle 5 and entered next cycle	71
Cycle 6	**n=71**
Patient discontinued after completion of Cycle 6; reason provided below:	65
Completed chemotherapy	64
Patient withdrew consent	1
Patient completed Cycle 6 and entered next cycle	5
Patient discontinued prior to completion of Cycle 6; reason provided below:	1
Patient discontinued for other reason	1
Cycle 7	**n=5**
Patient completed Cycle 7	5
Although patients are counted only once within a Treatment Cycle, patients may be counted in more than one Treatment Cycle. Patients are counted within a Treatment Cycle based on the earliest discontinuation reason for that patient.	

12. Diagnosis and main criteria for inclusion:

Men and women ≥18 years of age with a diagnoses of breast cancer requiring treatment with one of the following non-cisplatin moderately emetogenic chemotherapy regimens: IV cyclophosphamide (750 to 1500 mg/m^2 ± 5%), IV cyclophosphamide (500 to 1500 mg/m^2 ± 5%) and IV doxorubicin (≤60 mg/m^2 ± 5%), or IV cyclophosphamide (500 to 1500 mg/m^2 ± 5%) and IV epirubicin (≤100 mg/m^2 ± 5%).

13. Test product and reference therapy (if applicable); dose and mode of administration; batch number:

The base study (Cycles 1-4) had 2 treatment groups:

Aprepitant Regimen = ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg[†] P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3.

Standard Regimen = ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.

[†]Patients in the Aprepitant Regimen group received a lower dose of dexamethasone to account for a previously observed ~2 fold increase in the dexamethasone plasma levels associated with aprepitant compared to those in the control group.

Both the aprepitant and placebo, dexamethasone and placebo as well as the ondansetron placebo were manufactured by Merck & Co., Inc., West Point, Pennsylvania. Ondansetron was manufactured by GlaxoSmithKline in the United Kingdom.

The extension (Cycles 5-7) was open-label:

Day 1: Aprepitant 125 mg PO + ondansetron[‡] 8 mg PO twice daily + dexamethasone[‡] 12 mg PO

Days 2-3: Aprepitant 80 mg PO QD

[‡]The health care provider followed their clinic practice procedure to supply the dexamethasone 4 mg and ondansetron 8 mg tablets.

Aprepitant was manufactured by Merck & Co., Inc., West Point, Pennsylvania.

14. Duration of treatment:

Cycles 1-4: Aprepitant Regimen for 3 days (aprepitant 125 mg Day 1 and aprepitant 80 mg Days 2 and 3) in combination with ondansetron (Days 1 to 3) and dexamethasone (Day 1).

Cycles 5-7: Aprepitant Regimen for 3 days (aprepitant 125 mg Day 1 and aprepitant 80 mg Days 2 and 3) in combination with ondansetron (Day 1) and dexamethasone (Day 1).

15. Criteria for Evaluation:

Clinical response was evaluated with a patient diary that was completed daily for 5 days after the administration of chemotherapy. The diary captured all emetic episodes, all use of rescue therapy, and a daily nausea severity assessment. Patients were monitored for adverse experiences and tolerability at scheduled visits that occurred between Days 6 and 8 and Days 14 and 29 post chemotherapy. The primary endpoint assessed was the proportion of patients with Complete Response in the overall phase in Cycle 1, defined as no emesis and no use of rescue therapy for treatment of either nausea or emesis in the 120 hours following the initiation of chemotherapy in Cycle 1.

In the optional multiple-cycle extension, the patient diary was used to capture the daily nausea

severity assessment for 5 days after the administration of chemotherapy for each cycle that the patient entered. In addition, on Day 6, the patient recorded whether or not any emetic episodes or nausea occurred since the initiation of chemotherapy as well as any use of rescue therapy (only taken for treatment of established nausea or emesis).
In the open-label multiple-cycle extension (Cycles 5-7) the primary endpoint was the percentage of patients reporting drug-related adverse experiences. To further investigate aprepitant safety profile the following factors were tabulated: the proportion of patients with drug related adverse experience, the proportion of patients discontinuing due to a drug-related adverse experiences, and the proportion of patients with an adverse experience.

16. Statistical methods:

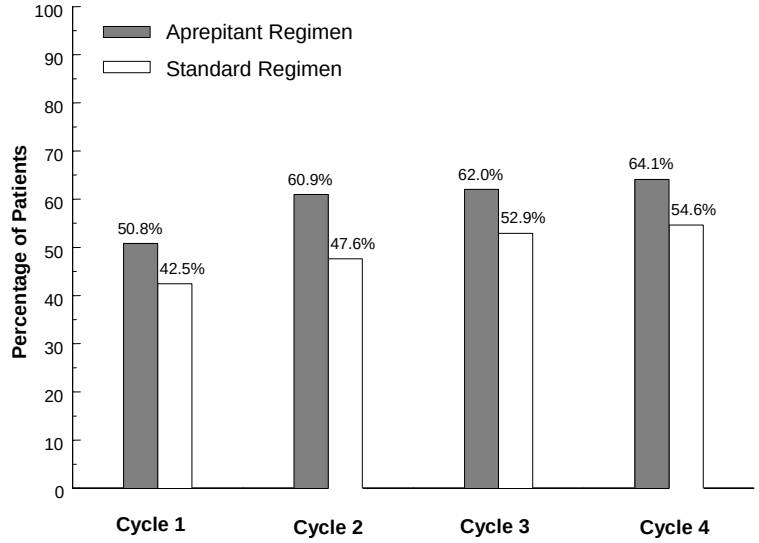
Efficacy (Cycle 1 Data): Primary analyses were based on a modified intention-to-treat (mITT) approach. In addition, a supportive per-protocol analysis was done for the primary efficacy parameter. Results are displayed for each endpoint by treatment group and phase (overall, acute, delayed, as well as 0 to 72 hours for nausea endpoints). With 375 evaluable patients per regimen and assuming a true response rate with the Standard Regimen of 52%, this study would have ~80% power to detect the superiority of the Aprepitant Regimen, if the true Aprepitant Regimen effect was 10 percentage points higher than the Standard Regimen. If the true difference was 12 percentage points, the power would be ~90%.

17. Summary:

RESULTS:

Clinical Efficacy (Cycle 1-4): The Aprepitant Regimen was significantly improved compared with the Standard Regimen with respect to the primary endpoint of Complete Response. During the multiple-cycle extension (Cycles 2-4) the treatment advantage seen with the Aprepitant Regimen over the Standard Regimen in terms of Complete Response was maintained.

Percentage of Patients with a Complete Response† in Cycles 1 to 4 by Treatment Group
(Modified Intention-to-Treat Population)



	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Aprepitant (N)	433	379	358	343
Standard (N)	424	355	325	304

†Complete Response: no emesis and no use of rescue therapy

Safety (Cycle 1 Data): The adverse experience profile was consistent with a population of patients receiving moderately emetogenic chemotherapy. The number of patients with drug-related adverse experiences, serious adverse experiences and adverse experiences resulting in discontinuation were very similar in the 2 treatment groups in Cycle 1. A summary of clinical and laboratory adverse experiences for Cycle 1, Cycles 2-4 and the open- label extension (Cycles 5-7) are presented in the following tables. No patient discontinued due to a laboratory adverse experience in any cycle.

Clinical and Laboratory Adverse Experience Summary—(Cycle 1)				
	Aprepitant Regimen (N=438)		Standard Regimen (N=428)	
	n	(%)	n	(%)
Clinical Adverse Experiences				
Number (%) of patients:				
With one or more AE	320	(73.1)	320	(74.8)
With no AE	118	(26.9)	108	(25.2)
With drug-related AE[†]	94	(21.5)	84	(19.6)
With serious AE	15	(3.4)	18	(4.2)
With serious drug-related AE	2	(0.5)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to AE	7	(1.6)	5	(1.2)
Discontinued due to drug-related AE	5	(1.1)	2	(0.5)
Discontinued due to serious AE	1	(0.2)	2	(0.5)
Discontinued due to serious drug-related AE	1	(0.2)	0	(0.0)
Laboratory Adverse Experiences				
Number (%) of patients:				
With at least one laboratory test postbaseline	436		426	
With one or more AE	77	(17.7)	75	(17.6)
With no AE	359	(82.3)	351	(82.4)
With drug-related AE[†]	4	(0.9)	8	(1.9)
With serious AE	0	(0.0)	0	(0.0)
With serious drug-related AE	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)

[†]Determined by the investigator to be possibly, probably, or definitely study drug related.
N = Number of randomized Cycle 1 patients in each treatment group, AE = adverse experience

Clinical and Laboratory Adverse Experience Summary Multiple-Cycle Patients (Cycles 2 to 4)		
Clinical Adverse Experiences	Aprepitant Regimen N=385	Standard Regimen N=359
Event Category	n (%)	n (%)
With one or more AE	308 (80.0)	260 (72.4)
With no AE	77 (20.0)	99 (27.6)
With drug-related AE†	63 (16.4)	57 (15.9)
With serious AE	17 (4.4)	13 (3.6)
With serious drug-related AE	1 (0.3)	1 (0.3)
Who died	1 (0.3)	0 (0.0)
Discontinued due to AE	7 (1.8)	4 (1.1)
Discontinued due to drug-related AE	3 (0.8)	1 (0.3)
Laboratory Adverse Experiences		
Event Category	n (%)	n (%)
With at least one lab test postbaseline	385	359
With one or more AE	74 (19.2)	65 (18.1)
With no AE	311 (80.8)	294 (81.9)
With drug-related AE†	4 (1.0)	7 (1.9)
With serious AE	0 (0.0)	1 (0.3)
With serious drug-related AE	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)

† Determined by the investigator to be possibly, probably or definitely drug related..
N = Number of randomized patients who entered cycles 2 to 4 in each treatment group, AE = adverse experience

Clinical and Laboratory Adverse Experience Summary - Cycles 5 to 7 (Open-Label Extension)	
Clinical Adverse Experiences	Aprepitant Regimen N=75
	n (%)
With one or more AE	37 (49.3)
With no AE	38 (50.7)
With drug-related† AE	5 (6.7)
With serious AE	1 (1.3)
With serious drug-related adverse experiences	0 (0.0)
Who died	0 (0.0)
Discontinued due to AE	0 (0.0)
Discontinued due to drug-related AE	0 (0.0)
Discontinued due to serious AE	0 (0.0)
Discontinued due to serious drug-related AE	0 (0.0)
Laboratory Adverse Experiences	
	n (%)
With at least one laboratory test postbaseline	75
With one or more AE	4 (5.3)
With no AE	71 (94.7)
With drug-related† AE	0 (0.0)
With serious drug-related AE	0 (0.0)
Who died	0 (0.0)
† Determined by the investigator to be possibly, probably or definitely drug related. N = Number of randomized patients who entered the open-label multiple-cycle extension, AE = adverse experience	
18. Date of the report: 17-Mar-08	
19. Contact: Sponsor National Service Center 1.800.672.6372	