1 Study Synopsis

Name of Sponsor/Company: Helsinn Healthcare SA	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Test Drug/ Investigational Product: Aloxi®, Onicit®, Paloxi®	Volume:	
Name of Active Ingredient: Palonosetron hydrochloride	Page:	
Title of Study: Multicenter, Phase IV, Open-Label, Uncontrolled Study to Assess the Efficacy and Safety of a Single Intravenous Dose of Palonosetron 0.25 mg (Aloxi®, Onicit®, Paloxi®) in the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients with Non-Hodgkin's Lymphomas Undergoing Repeated Cycles of Moderately Emetogenic Chemotherapy		
Investigators: In this study 18 investigators enrolled at least one patient.		
Study Centers: In total, 18 study centers enrolled at least one patient each: four centers in the Czech Republic, four centers in Romania, two centers in Germany, three centers in Italy and five centers in the United States (US).		
Publication (Reference): None	**Phase of Development:** IV	
Studied Period: 20 January 2010 to 10 March 2011		
Objectives: The main objective was to assess the efficacy of single doses of intravenous (IV) palonosetron 0.25 mg (Aloxi®, Onicit®, Paloxi®) in individual study cycles and the maintenance of such efficacy through repeated and consecutive study cycles, when administered for the prevention of Chemotherapy Induced Nausea and Vomiting (CINV) to patients with Non-Hodgkin's Lymphomas receiving repeated (a minimum of two up to a maximum of four) and consecutive single-day moderately emetogenic chemotherapy (MEC) cycles. A further objective was to evaluate the safety of IV palonosetron in initial and repeated consecutive MEC cycles for up to four study cycles.		
Methodology: This multicenter, open-label, uncontrolled Phase IV study was designed to assess the efficacy and safety of single 0.25 mg IV doses of palonosetron (Aloxi®, Onicit®, Paloxi®) in the prevention of CINV during up to four repeated and consecutive single-day MEC cycles, administered to patients with Non-Hodgkin's Lymphomas. Patients attended the study center on three occasions for study Cycle 1: Screening Visit (Visit 1, Days -15 to -1), Visit 2 (Day 1) and Visit 3 (Days 8 to 10), and were contacted by telephone on Day 2. Patients attended the study center on the same occasions (and were contacted by telephone on Day 2) for study Cycles 2, 3 and 4, except that Visit 1 (Days -3 to 1) of the repeated study cycles involved only some of the assessments performed at the Screening Visit. Patients were allowed to participate in the study for a minimum of two and at most four study cycles. The study medication was to be administered in consecutive MEC cycles; MEC was to be scheduled on Day 1 of each cycle only. No MEC was allowed between Days 2 to 5 of each cycle, and no highly emetogenic chemotherapy was allowed during the overall study period. In addition to study treatment, rescue medication for treatment of nausea and vomiting was permitted after the start of administration of the first most emetogenic chemotherapeutic agent, at the discretion of the Investigator. Rescue medication of any kind was allowed at the discretion of the Investigator; nevertheless anti-emetics		

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other than 5-hydroxytryptamine (5-HT_3, serotonin) receptor antagonists were recommended.
Commercial Palonosetron (Aloxi®, Onicit® or Paloxi®) was not allowed as rescue medication.

Number of Subjects (Planned and Analyzed): A total of 200 patients were planned to be treated in this study. Due to enrollment difficulties, only 88 patients were enrolled by the planned study termination date (January 2011).
Eighty-eight patients were treated in at least one study cycle. All 88 patients were included in both analysis sets (safety set [SAF]) and full analysis set [FAS]), and all patients were eligible for subgroup analysis.

Diagnosis and Main Criteria for Inclusion: Patients had to meet all of the following criteria to be included in the study, or to continue participating in any of the repeated study cycles:

1. Male or female, ≥ 18 years of age.
2. Histologically or cytologically confirmed Non-Hodgkin's Lymphoma.
3. Patient scheduled to receive single-day MEC as one of the following regimens (at each study cycle) in at least two repeated and consecutive chemotherapy cycles:
   - CHOP or R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, with or without Rituximab);
   - ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, leucovorin and prednisone).

Consecutive chemotherapeutic cycles had to employ the same chemotherapeutic regimen. This could include changes in dose (adjustments of dose) of the MEC agent(s) or discontinuation of low, minimal or non-emetogenic concomitant chemotherapeutic agents as clinically appropriate, with no highly emetogenic agents added.

4. Naïve to cancer chemotherapy (i.e. the patient had no chemotherapeutic history).
5. A Karnofsky Performance Status of ≥ 50%, at each study cycle.
6. Signed written informed consent (with additional legal representative's consent or parent's consent if required).
7. Patient with a known hepatic, renal or cardiovascular impairment, including cardiac conduction interval abnormalities, and scheduled to receive the above mentioned chemotherapeutic agents, could be enrolled in this study or continue the participation in each of the repeated study cycles at the discretion of the Investigator.
8. Female patient of childbearing potential had to use reliable contraceptive measures with a negative urine pregnancy test before any study treatment administration.

Additionally, to be enrolled and treated in any of the study cycles, patients were not to have taken any anti-emetic medication within 24 hours before the administration of the study medication, nor having had vomiting, retching or National Cancer Institute (NCI) Common Toxicity grade 2 or 3 nausea in the 24 hours preceding chemotherapy. Treatment with commercial palonosetron was not allowed during 2 weeks before study

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drug administration.		
Test Product, Dose and Mode of Administration, Batch Number: Palonosetron (0.25 mg) IV administered as a 30 second bolus injection 30 minutes before the start of the first most emetogenic chemotherapeutic agent on Day 1 of study Cycle 1, and on Day 1 of subsequent study cycles for a minimum of two up to a maximum of four consecutive study cycles. The lot number was [redacted].		
Duration of Treatment: Patients were allowed to continue in the protocol until a maximum of four consecutive study cycles had been performed. Once the last patient had been enrolled in this study, all patients with less than 4 study cycles performed were allowed to complete the maximum number of study cycles up to two weeks after the last enrolled patient had completed the second study cycle. The duration of an individual study cycle was approximately 10 days, with the exception of Study Cycle 1 which could have been longer (up to a maximum of 25 days) due to the allowed 2 weeks screening period.		
Reference Therapy, Dose and Mode of Administration, Batch Number: No reference therapy was used in this study.		
Criteria for Evaluation:		
Efficacy: The primary efficacy endpoint was the overall complete response (CR; defined as no emetic episode and no rescue medication) for the 0 to 120 hours interval after the start of the emetogenic chemotherapy. Secondary efficacy endpoints were the CR for the 0 to 24 hours (acute phase) and the >24 to 120 hours (delayed phase) intervals, the severity of nausea, complete protection, percentage of patients without emesis, percentage of patients without rescue medication, all during the 0 to 24 hours, >24 to 120 hours and 0 to 120 hours time intervals. Additional endpoints were the time to treatment failure and the evaluation of the patient's health-related Quality of Life (QoL) using the Modified Functional Living Index-Emesis (FLIE) questionnaire.		
Safety: Safety variables assessed were adverse events (AEs), laboratory parameters, vital signs, physical examination, and 12-lead electrocardiograms (ECGs).		
Statistical Methods: The SAF was defined as all patients with at least one cycle of chemotherapy with administration of IV palonosetron 0.25 mg and with at least one safety assessment after treatment. Chemotherapy cycles without administration of study drug and/or without any safety assessment after treatment were excluded from the analysis. The FAS was defined as all patients with at least one cycle of at least MEC (i.e. moderately or highly emetogenic chemotherapy) and with administration of IV palonosetron 0.25 mg. Cycles without administration of at least MEC and/or study drug were excluded from the analysis. All analyses of efficacy parameters were performed for the FAS only. The results were interpreted in a descriptive manner. Subgroup analyses were provided for all efficacy parameters by region (Western Europe (defined as Italy and Germany), Romania, Czech Republic and US), gender and by age groups (<65 years,≥65 years). Efficacy data were also listed.		

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The proportion of patients achieving CR for the 0 to 120 hours interval (and 95% confidence intervals [CIs]) was summarized for each study cycle and for all cycles. An additional analysis of the primary endpoint was done by region, gender and age groups.

The proportion of complete responders (and 95% CIs) during the acute phase (0 to 24 hours interval) and delayed phase (>24 to 120 hours interval) was summarized for each study cycle and for all cycles. In addition, daily intervals (>24 to 48 hours, >48 to 72 hours, >72 to 96 hours, >96 to 120 hours) were analyzed for all efficacy parameters. For the severity of nausea for each time period, descriptive statistics were performed for each study cycle. For 0 to 120 hours and >24 to 120 hours time periods, the mean severity of nausea as well as the maximum severity of nausea were calculated. For each time period, the proportion of patients with complete protection (and 95% CIs) was summarized for each study cycle and for all cycles. Complete protection was defined as “no emesis, no rescue therapy and no significant nausea”, with “no significant nausea” being defined as “nausea intensity below 25 mm on the 100 mm horizontal visual analogue scale (VAS)”. For each time period, the proportion of patients without emesis, without nausea (defined as nausea <5 mm on 100 mm VAS) and without rescue medication was summarized for each study cycle. The severity of nausea (in categories <5, 5 to <25, ≥25 mm on 100 mm VAS) was analysed, and proportions of patients in each category were calculated. Moreover, for each time period the 95% CIs were provided for the proportion of patients without emesis and without rescue medication. Rescue medication was listed and summarized.

Kaplan-Meier estimates were used to present the time to treatment failure (time to first emetic episode or to administration of rescue medication, whichever occurred first) for each study cycle and for all cycles. Associated 95% CIs for median time were presented for each study cycle. For the modified FLIE, the vomiting and nausea domain scores, and total score, were summarized for each cycle and for all cycles. Additional efficacy analyses were performed to explore the maintenance of efficacy through repeated and consecutive study cycles.

All analyses of safety parameters were performed for the safety set only. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0, to provide a system organ class (SOC) and a preferred term (PT) for each event.

The results were interpreted in a descriptive manner. Subgroup analyses of several AE tables by region, age group and sex were provided. Clinical laboratory data were summarized using frequency tables for values within/outside reference ranges and shift tables were used to evaluate categorical changes of clinical laboratory data versus baseline. Safety data were also listed.

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Summary – Conclusions:

Efficacy Results: Patients showed CR for the majority of cycles.

Number and percentage of patients with a complete response, by study cycle and overall

Interval	Cycle 1, N = 88		Cycle 2, N = 82		Cycle 3, N = 78		Cycle 4, N = 69		Total, N = 317	
(hours)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0 – 120	**60**	**(68.2)**	**66**	**(80.5)**	**61**	**(78.2)**	**56**	**(81.2)**	**243**	**(76.7)**
0 – 24	68	(77.3)	69	(84.1)	64	(82.1)	58	(84.1)	259	(81.7)
>24 – 48	77	(87.5)	79	(96.3)	75	(96.2)	67	(97.1)	298	(94.0)
>48 – 72	80	(90.9)	80	(97.6)	76	(97.4)	66	(95.7)	302	(95.3)
>72 – 96	84	(95.5)	80	(97.6)	76	(97.4)	67	(97.1)	307	(96.8)
>96 – 120	82	(93.2)	78	(95.1)	74	(94.9)	67	(97.1)	301	(95.0)
>24 – 120	73	(83.0)	77	(93.9)	72	(92.3)	65	(94.2)	287	(90.5)

N = total number of patients, n = number of patients with data available

For the overall interval (0 to 120 hours), the percentage of patients with a CR increased from 68.2% at Cycle 1 to 80.5% at Cycle 2 with little change in the following two cycles.
For the acute phase interval (0 to 24 hours), the percentage of patients with a CR increased from 77.3% at Cycle 1 to 84.1% at Cycle 2, with little change thereafter. In the delayed phase interval (>24 to 120 hours), the percentage of patients with a CR was higher than in the acute phase; it increased from 83.0% at Cycle 1 to 93.9% at Cycle 2. At Cycles 3 and 4, values were again similar to Cycle 2. At Cycle 1, the daily CR rates within the >24 to 120 hours interval tended to increase with time from 87.5% during the >24 to 48 hours interval to 95.5% during the >72 to 96 hours interval and slightly decreased in the last interval. At Cycles 2, 3 and 4, the percentages CR for the daily intervals after Day 1 were overall similar.

Mean (SD) Severity of Nausea (100 mm VAS) by Cycle

Interval	Cycle 1 N = 88	Cycle 2 N = 82	Cycle 3 N = 78	Cycle 4 N = 69	Total N = 317
(hours)	n=88	n=82	n=78	n=69	n=317
0 – 24	7.4 (19.35)	5.6 (14.90)	5.0 (12.50)	3.8 (8.84)	5.6 (14.72)
>24 – 120 (mean)[a]	6.95 (17.570)	3.73 (9.664)	3.18 (8.283)	3.21 (6.909)	4.37 (11.769)
>24 – 120 (max)[a]	11.34 (21.852)	5.60 (14.379)	4.68 (10.030)	5.19 (11.929)	6.88 (15.729)
0 – 120 (mean)[a]	7.03 (17.387)	4.08 (9.455)	3.53 (8.455)	3.31 (6.914)	4.60 (11.671)
0 – 120 (max)[a]	13.16 (22.994)	7.71 (18.316)	6.49 (13.424)	6.10 (12.824)	8.57 (17.869)

N = total number of patients, n = number of patients with data available, SD = standard deviation; VAS = visual analogue scale
[a] Patients' mean/maximum values during given time interval; the VAS scores (in mm) were categorized as: <5: no nausea, 5 to <25: no significant nausea, ≥25: nausea

For the acute phase, the severity of nausea on the VAS was 7.4 mm, i.e. the average score fell in the no significant nausea interval (but individual values ranged from 0 to

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95 mm) at Cycle 1 and decreased with subsequent cycles to 3.8 mm at Cycle 4, i.e. the average score fell in the no nausea interval (ranges were 0 to 44 mm). Similarly, in the delayed phase, the patients' mean severity of nausea decreased from 6.95 mm at Cycle 1 (no significant nausea) to 3.21 mm at Cycle 4 (no nausea). Using the patients' maximum values, the mean severity of nausea decreased from 11.34 mm at Cycle 1 to 5.19 mm at Cycle 4 (no significant nausea).
For the entire 0 to 120 hours interval, the patients' mean severity of nausea had decreased mostly in Cycle 2 and stayed relatively stable thereafter. For the patients' maximum values, similar changes over time were seen.

Nausea scores by category and cycle

Interval		Cycle 1 N = 88		Cycle 2 N = 82		Cycle 3 N = 78		Cycle 4 N = 69		Total N = 317	
(hours)	Nausea	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0 – 24	<5	69	(78.4)	63	(76.8)	61	(78.2)	61	(88.4)	254	(80.1)
	5 - <25	14	(15.9)	14	(17.1)	14	(17.9)	4	(5.8)	46	(14.5)
	≥25	5	(5.7)	5	(6.1)	3	(3.8)	4	(5.8)	17	(5.4)
>24 – 120	<5	54	(61.4)	62	(75.6)	62	(79.5)	55	(79.7)	233	(73.5)
(max)[a]	5 - <25	21	(23.9)	16	(19.5)	13	(16.7)	9	(13.0)	59	(18.6)
	≥25	13	(14.8)	4	(4.9)	3	(3.8)	5	(7.2)	25	(7.9)
0 – 120	<5	49	(55.7)	59	(72.0)	56	(71.8)	54	(78.3)	218	(68.8)
(max)[a]	5 - <25	24	(27.3)	16	(19.5)	17	(21.8)	9	(13.0)	66	(20.8)
	≥25	15	(17.0)	7	(8.5)	5	(.4)	6	(8.7)	33	(10.4)

N = total number of patients, n = number of patients with data available
[a] Patients' maximum values during given time interval; the VAS scores (in mm) were categorized as: <5: no nausea, 5 to <25: no significant nausea, ≥25: nausea

In all time intervals, including the daily, 24-hours intervals (data not shown in the above table), patients had nausea scores <5 mm for the largest proportion of cycles. For the acute phase, the percentage of patients with nausea scores <5 mm was 78.4% at Cycle 1 and 88.4% at Cycle 4. The percentage of patients with nausea scores of 5 to <25 mm was approximately 17% at Cycles 1 to 3 and decreased to 5.8% at Cycle 4. The percentage of patients with nausea scores ≥25 mm was low (4-6%).
For the delayed phase interval and the overall interval, patients' maximum values were evaluated. For the delayed phase, the percentage of patients with maximum nausea scores <5 mm increased from 61.4% at Cycle 1 to 79.5% at Cycle 3 and remained stable thereafter. The percentage of patients with maximum nausea scores of 5 to <25 mm decreased from 23.9% at Cycle 1 to 13.0% at Cycle 4. The percentage of patients with maximum nausea scores ≥25 mm decreased from 14.8% at Cycle 1 to 4.9% at Cycle 2 and remained relatively low thereafter.
For the overall interval, the percentage of patients with maximum nausea scores <5 mm increased from 55.7% at Cycle 1 to 72.0% at Cycle 2, and with further small increases thereafter. The percentage of patients with nausea scores 5 to <25 mm decreased from 27.3% at Cycle 1 to approximately 20% at Cycles 2 and 3, with a

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further decrease to 13.0% at Cycle 4. The percentage of patients with nausea scores ≥25 mm decreased from 17.0% at Cycle 1 to 8.7% at Cycle 4.

Complete Protection, by Cycle										
Interval	Cycle 1, N = 88		Cycle 2, N = 82		Cycle 3, N = 78		Cycle 4, N = 69		Total, N = 317	
(hours)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0 – 24	67	(76.1)	66	(80.5)	62	(79.5)	56	(81.2)	251	(79.2)
>24 – 120	67	(76.1)	75	(91.5)	70	(89.7)	62	(89.9)	274	(86.4)
0 -120	55	(62.5)	64	(78.0)	57	(73.1)	53	(76.8)	229	(72.2)

N = total number of patients, n = number of patients with data available

The percentage of patients with complete protection in the acute phase increased from 76.1% at Cycle 1 to 80.5% at Cycle 2. In the delayed phase, the percentage of patients with complete protection increased from 76.1% at Cycle 1 to 91.5% at Cycle 2. In the overall interval, the percentage of patients with complete protection increased from 62.5% at Cycle 1 to 78.0% at Cycle 2. For all intervals, the percentage of patients with complete protection at Cycles 3 and 4 was similar to that at Cycle 2.

No Emesis, by Cycle										
Interval	Cycle 1, N = 88		Cycle 2, N = 82		Cycle 3, N = 78		Cycle 4, N = 69		Total, N = 317	
(hours)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0 – 24	80	(90.9)	77	(93.9)	75	(96.2)	65	(94.2)	297	(93.7)
>24 – 120	78	(88.6)	78	(95.1)	73	(93.6)	66	(95.7)	295	(93.1)
0 - 120	76	(86.4)	75	(91.5)	72	(92.3)	64	(92.8)	287	(90.5)

N = total number of patients, n = number of patients with data available

The percentage of patients with no emesis in the acute phase was 90.9% at Cycle 1 and slightly higher in subsequent cycles. In the delayed phase, the percentage of patients without emesis increased from 88.6% at Cycle 1 to 95.1% at Cycle 2. In the overall interval, the percentage of patients without emesis increased from 86.4% at Cycle 1 to 91.5% at Cycle 2. For all intervals, the percentage of patients without emesis at Cycles 3 and 4 was similar to that at Cycle 2.

No Rescue medication, by Cycle										
Interval	Cycle 1, N = 88		Cycle 2, N = 82		Cycle 3, N = 78		Cycle 4, N = 69		Total, N = 317	
(hours)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0 – 24	73	(83.0)	72	(87.8)	67	(85.9)	59	(85.5)	271	(85.5)
>24 – 120	79	(89.8)	79	(96.3)	76	(97.4)	67	(97.1)	301	(95.0)
0 - 120	67	(76.1)	69	(84.1)	66	(84.6)	57	(82.6)	259	(81.7)

N = total number of patients, n = number of patients with data available

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The percentage of patients not using any rescue medication in the acute phase was 83.0% at Cycle 1 and slightly increased to 87.8% at Cycle 2. In the delayed phase, the percentage of patients not using rescue medication increased from 89.8% at Cycle 1 to 96.3% at Cycle 2. In the overall interval, the percentage of patients not using rescue medication increased from 76.1% at Cycle 1 to 84.1% at Cycle 2. For all cycles, the median time to treatment failure was more than 120 hours.

The mean mm (using a 100 mm VAS) and points scores for the Modified FLIE for nausea and vomiting and the corresponding total score showed little differences at individual cycles. Maximum attainable scores in mm were 900 mm for nausea and vomiting each, and 1800 mm in total; maximum attainable scores in points were 63 for nausea and vomiting each and 126 points in total.
Mean scores were high indicating good ability to maintain daily life, and for the total number of cycles were 844.20 mm (nausea), 867.82 mm (vomiting) and 1711.49 mm (total). The mean scores for the total number of cycles were 59.65 points (nausea), 61.07 points (vomiting) and 120.69 points (total).

The main outcomes of the subgroup analyses were as follows:

Complete response: Overall, relatively more male than female patients showed a CR and slightly more patients ≥65 years of age than patients <65 years of age showed a CR. There was a slightly higher percentage of patients with a CR for the 0 to 120 hours interval in the Romanian centers compared to that in the Czech Republic centers, at all study cycles and compared to that in West-European (Italian and German) centers at 2 of the 4 study cycles.

Severity of nausea (100 mm VAS): The severity of nausea was clearly higher in female patients compared to male patients, at all study cycles, and at all time intervals investigated. At Cycle 1 the severity of nausea was clearly higher in patients ≥65 years of age than in younger patients while at Cycles 2 to 4 the severity of nausea tended to be higher in younger patients. The severity of nausea (100 mm VAS) was observed to be higher in Romanian and West-European centers than in the Czech Republic centers at each cycle, particularly at Cycle 1 at West-European centers and for virtually all time intervals investigated.

Severity of nausea (proportions): There were generally more male patients than female patients with nausea scores <5 mm (no nausea), and more female patients than male patients with nausea ≥5 and <25 mm (non significant nausea), at all time intervals and study cycles investigated. In both age groups, the percentage of patients with a nausea score <5 mm (no nausea) was clearly higher than the percentage of patients with a nausea score ≥5 and <25 mm (non significant nausea). Overall, relatively more, older than younger patients had scores in the low nausea category (<5 mm, no nausea). In conjunction, relatively more younger than older patients had

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scores in the higher nausea categories (≥5 and <25 mm, and ≥25 mm). In the Czech Republic centers, there were relatively more patients with nausea scores <5 mm (no nausea) than in Romanian and West-European centers, particularly in Cycles 1 and 2.

Safety Results: Overall, 78.4% of patients experienced a total of 301 treatment emergent AEs (TEAEs). Relatively more female patients (91.4%) than male patients (69.8%) experienced at least one TEAE. TEAEs in the SOC Blood and lymphatic system disorders were the most commonly reported TEAEs followed by TEAEs in the SOCs gastrointestinal disorders and infections and infestations. At the PT level, anemia, neutropenia, leukopenia, constipation and alopecia were the most frequent events; such events are in line with the patient's pathology and pharmacological treatments administered during the study (cytotoxic chemotherapy). The percentage of patients with TEAEs steadily decreased from Cycle 1 (58.0%) to Cycle 4 (32.4%). For the first cycle, TEAEs in the SOC gastrointestinal disorders were the most frequently reported ones. The incidence of gastrointestinal disorders decreased continuously from the first to the last Study Cycle. TEAEs in the SOC blood and lymphatic system disorders were the second most frequently reported TEAEs in Cycle 1 and were the most frequent TEAEs in Cycle 2 to Cycle 4. On the PT level, the gastrointestinal TEAEs constipation, diarrhea, dyspepsia, flatulence, irritable bowel syndrome, nausea and vomiting were most frequently observed, in Cycle 1, compared to other cycles. TEAEs of the SOC blood and lymphatic system disorders, i.e. anemia, neutropenia and leukopenia, were among the most frequent TEAEs in all cycles.

A relationship to the study drug was found for a limited number of TEAEs reported by a small portion of patients (8.0%). Only 4.5% of all patients had TEAEs that were considered possibly related, and 3.4% had probably related TEAEs. No patient had a TEAE considered to be definitely related to the study drug. The highest percentage of patients reporting drug-related TEAE at any one cycle was 5.7%, at Cycle 1. General disorders and administration site conditions were the only SOCs with more than two patients experiencing drug-related TEAEs. At the PT level, constipation and fatigue were the only drug-related TEAEs experienced by two patients; all other drug-related TEAEs were experienced by single patients only. During the overall study period at most one or two cycles with drug-related TEAEs per cycle were documented per SOC or PT.

The majority of patients experienced at least one TEAE of mild or moderate intensity during the entire study period. Of all patients, 17.0% experienced severe TEAEs. The percentage of patients with severe TEAEs decreased continuously from Cycle 1 (9.1%) to Cycle 4 (1.5%). Throughout all cycles the distribution of mild, moderate and severe TEAEs was similar, i.e. in the majority of cycles TEAEs were mild, followed by moderate; severe TEAEs occurred in a few cycles only. A discrepancy existed between the exact number of severe and moderate AEs in the listings and in the Helsinn Safety data base, but this did not influence the overall conclusions of this study.

Two patients died during this study. One patient died due to bronchopneumonia in

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Cycle 3. Another patient died due to cardiac arrest in Cycle 1. Both events were assessed by the Investigator as not related to the study drug.

A total of 17 patients (19.3%) experienced 26 serious TEAEs during the study. All serious TEAEs were assessed as not related or unlikely related to study drug. Febrile neutropenia, leukopenia, pyrexia, gastroenteritis and interstitial lung disease were the serious TEAEs experienced by two patients. All other serious TEAEs occurred in single patients. The highest percentage of patients with serious TEAEs in any one cycle was observed at Cycle 1 (10.2%), followed by Cycle 3 (6.5%). In Cycle 2 and Cycle 4 serious TEAEs only occurred in two patients each (2.5% and 2.9%, respectively).

Five patients (5.7%) had TEAEs leading to study discontinuation; four of those patients had serious TEAEs leading to discontinuation (4.5% of all patients). Two patients were discontinued because of TEAEs classified in the SOCs blood and lymphatic system disorders, and infections and infestations. The remaining TEAEs leading to discontinuation occurred in individual patients only. Two patients discontinued the study due to TEAEs during the first cycle, three patients discontinued during the third cycle.

Hematology and blood chemistry values were generally normal both at baseline and at Visit 3 for the majority of cycles. Parameters mostly showing shifts from normal to below or above the reference range included hemoglobin, hematocrit, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, creatinine and alanine aminotransferase (ALT). Urinalysis values were also generally normal at baseline and at Visit 3.

There were no noteworthy differences between the individual cycles for systolic and diastolic blood pressure and pulse rate, and changes from baseline to Visit 3 were small for all three parameters.

At the physical examination only a small percentage of patients showed abnormalities for most body systems. The majority of ECG results were normal at baseline and at Visit 3; of the changes from normal at baseline to abnormal at Visit 3 most were assessed as not clinically significant.

Conclusion: The efficacy of single doses of IV palonosetron 0.25 mg in individual study cycles and the maintenance of efficacy through repeated and consecutive MEC cycles in patients with Non-Hodgkin's Lymphomas were shown in this study. For the majority of cycles, patients were complete responders in the overall 0 to 120 hours interval after the administration of the first most emetogenic chemotherapeutic agent as well as in the acute phase interval (0 to 24 hours) and the delayed phase interval (>24 hours to 120 hours). Continued efficacy in subsequent cycles was also shown by results of this and of other efficacy variables.

The analysis of TEAEs, laboratory values, vital signs and 12-lead ECG data did not raise any safety concern for the administration of IV palonosetron 0.25 mg in repeated and consecutive moderately emetogenic cycles of chemotherapy.

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