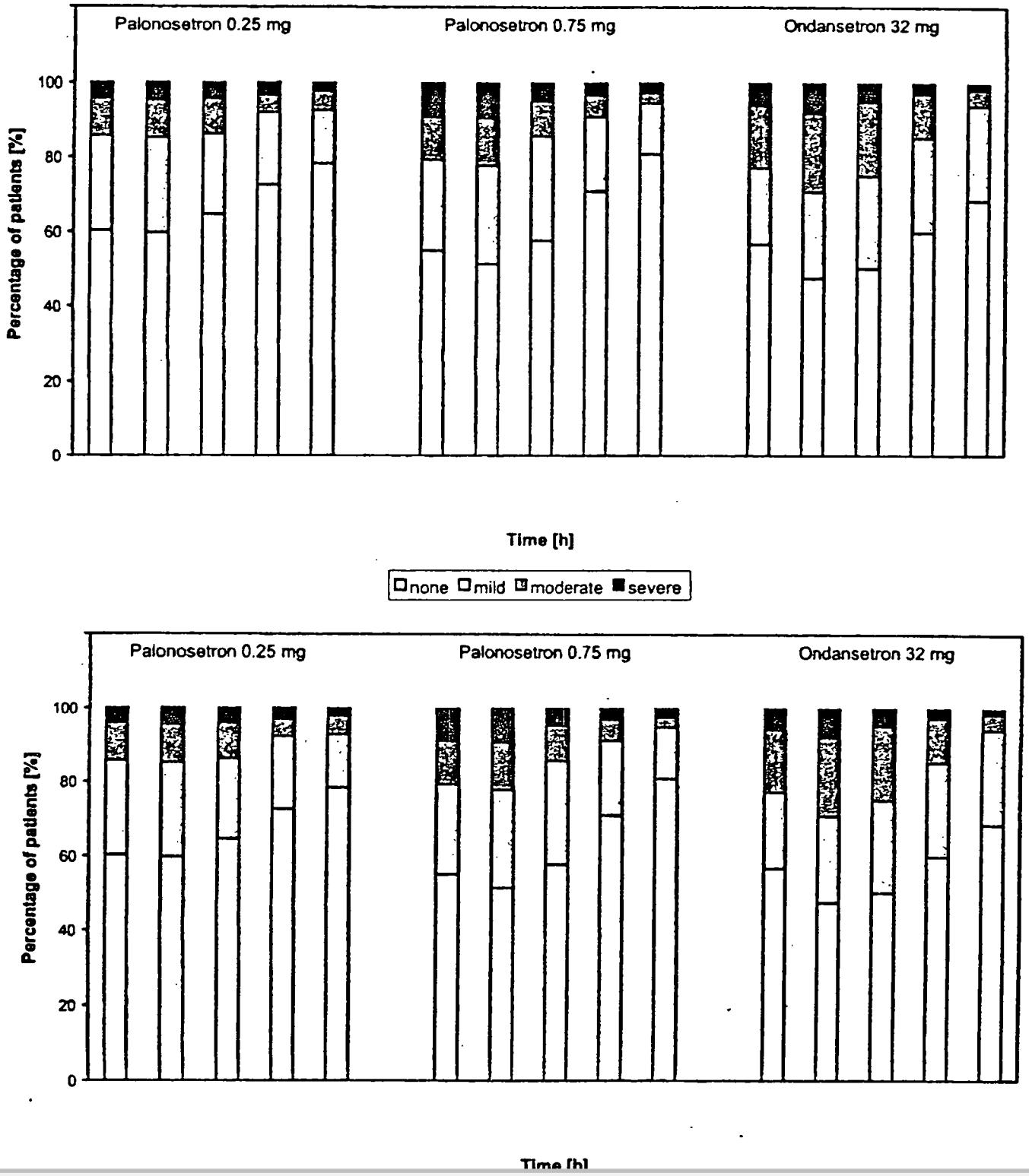
**FIGURE 1: Severity of nausea during Study Day 1, 2, 3, 4, and 5**
**PALO-99-03 (top), PALO-99-04 (bottom) (Scanned from figure 7.1.2.4-a,)**



***Medical Officer Comments:*** *For PALO 99-03, the rate of patients without nausea was highest in the palonosetron 0.25 mg group and lowest in the ondansetron group. For Day 1 the difference was not significant (p-value 0.318 using Kruskal-Wallis test). For Days 2,3,4,5 there was a statistically significant difference between groups in favor of the 0.25 mg dose of palonosetron. When pairwise testing (using the Wilcoxon test) was done with the 0.25 mg palonosetron group versus ondansetron statistically significant differences were seen on Day 2, 3, and 4. This is consistent with the pharmacologic properties of palonosetron, which has a longer half-life than ondansetron.*

*For PALO-99-04, the rate of patients without nausea was higher in the palonosetron groups compared to the dolasetron group. For Day 1 the difference was not significant. For Days 2,3,4, there was a statistically significant difference between groups in favor of the 0.25 mg dose of palonosetron. When pairwise testing (using the Wilcoxon test) was done with the 0.25 mg palonosetron group versus dolasetron, statistically significant differences were seen on Day 2, and 3 but not for Day 4 or 5.*

**Secondary Efficacy Endpoint – Time to Rescue Medication**

The median time to first use of rescue medication was greater than 120 hours for all groups in both studies. However, the sponsor did an analysis of the first quartile of patients and found that the time to first administration of rescue medication tended to be shorter in the dolasetron group. It is unclear what the clinical relevance of this finding is since this was an unplanned analysis. Overall, few patients took rescue mediation during this study. There was no statistical difference between treatment groups in the number of patients who took rescue medication for any study day.

**Secondary Efficacy Endpoint – Time to Treatment Failure**

The median time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first) was again greater than 120 hours for all groups in both studies. Analysis of the first quartile of patients found that the time to treatment failure was longest in the 0.25 mg Palonosetron group.

**Secondary Efficacy Endpoint – Quality of Life Questionnaire**

The quality of life was assessed by using a modified and validated Functional Living Index Emesis (FLIE). This consisted of 18 questions divided into 2 domains (nausea, and vomiting. The questions were assessed by using a visual analog scale (VAS). A high score reflects less impairment from nausea and vomiting. The following tables display the results for both PALO-99-03, and PALO-99-04 respectively.

**TABLE 21: PALO-99-03 - Quality of Life VAS scores for nausea and vomiting**

| Time Period (hours) | Palonosetron 0.25 mg (N=189) Median | Palonosetron 0.75 mg (N=189) Median | Ondansetron 32 mg (N=185) Median |
|---|---|---|---|
| **0-24 hours** | | | |
| Nausea | 872 | 866 | 851 |
| Vomiting | 900 | 897 | 899 |
| Overall score | 1587 | 1749 | 1721 |
| **24-96 hours** | | | |
| Nausea | 861 | 866 | 828 |
| Vomiting | 899 | 896 | 889 |
| Overall score | 1740 | 1734 | 1680 |

(Reference: Table 7.1.2.8-a ,page 126, Volume 117)

**TABLE 22: PALO-99-04 - Quality of Life VAS scores for nausea and vomiting**

| Time Period (hours) | Palonosetron 0.25 mg (N=189) Median | Palonosetron 0.75 mg (N=189) Median | Dolasetron 100 mg (N=191) Median |
|---|---|---|---|
| **0-24 hours** | | | |
| Nausea | 831 | 841 | 789 |
| Vomiting | 884 | 874 | 874 |
| Overall score | 1686 | 1700 | 1629 |
| **24-96 hours** | | | |
| Nausea | 826 | 833 | 728 |
| Vomiting | 882 | 885 | 873 |
| Overall score | 1672 | 1683 | 1599 |

(Reference: Table 7.1.2.8-a ,page 126, Volume 135)

***Medical Officer Comments:*** *For Study PALO-99-03, median quality of life scores were similar in all the treatment groups. Statistical testing found no difference between the groups for nausea, vomiting and the overall score during the 0-24 hours time period. There was statistical difference for the total score for the time period 24-96 hours between palonosetron 0.25 mg and ondansetron (p=0.014). No statistical difference was found between the higher dose of palonosetron and ondansetron,(p=0.130) nor between the 2 doses of palonosetron (p=0.369).*

*For Study PALO-99-04, again statistical testing found no difference between the groups for nausea, vomiting and the overall score during the 0-24 hours time period. There was statistical difference for the nausea score for the time period 24-96 hours between palonosetron 0.25 mg and dolasetron (p=0.031).*

Secondary Efficacy Endpoint -Global Satisfaction with Therapy

The global satisfaction of the patients with the anti-emetic therapy was recorded on a VAS for the entire 120-hour interval. Global satisfaction was evaluated daily. The results are shown in the following tables

**TABLE 23: PALO-99-03 - Global Satisfaction with Anti-emetic therapy (ITT cohort, N=563)**

| Time Period (hours) | Palonosetron 0.25 mg (N=189) Median | Palonosetron 0.75 mg (N=189) Median | Ondansetron 32 mg (N=185) Median |
|---|---|---|---|
| **Acute** | | | |
| 0-24 hours | 97 | 96 | 97 |
| **Delayed** | | | |
| 24-48 | 97 | 94 | 93 |
| 48-72 | 98 | 96 | 94 |
| 72-96 | 99 | 98 | 97 |
| 96-120 | 99 | 99 | 98 |

(Reference: Table 7.1.2.7-a, page 124, Volume 117)

**TABLE 24: PALO-99-04 - Global Satisfaction with Anti-emetic therapy (ITT cohort, N=569)**

| Time Period (hours) | Palonosetron 0.25 mg (N=189) Median | Palonosetron 0.75 mg (N=189) Median | Dolasetron 100 mg (N=191) Median |
|---|---|---|---|
| **Acute** | | | |
| 0-24 hours | 95 | 93 | 90 |
| **Delayed** | | | |
| 24-48 | 95 | 92 | 85 |
| 48-72 | 95 | 95 | 90 |
| 72-96 | 97 | 97 | 93 |
| 96-120 | 98 | 98 | 96 |

(Reference: Table 7.1.2.7-a, page 130, Volume 135)

***Medical Officer's Comments**: For PALO-99-03, a statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 3 (p=0.045) but not the other days (0.05). A pair wise test between 0.25 mg of palonosetron and ondansetron showed a significant difference (0.015) in favor to palonosetron for Day 3 also. No difference was seen between the two palonosetron groups or between 0.75 mg palonosetron and ondansetron.*

*For PALO-99-04, a statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 2 (p=0.008) but not the other days). A pairwise test between 0.25 mg of palonosetron and dolasetron showed a significant difference (0.022) in favor to palonosetron for Day 4.*

**Summary of Results for Secondary Efficacy Endpoints for PALO-99-03, and 99-04**

The table on the following pages displays a summary of the statistical analysis regarding the secondary efficacy endpoints.

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