AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

MAY 12-15, 2001

SAN FRANCISCO – USA

- **Reference**: Program/Proceedings American Society of Clinical Oncology, Vol. 20, Part 1 of 2, 2001
  Abstract no. 1595

- **Topic**: phase I trials, pk and safety, i.v. administration

- **Note**: abstract and poster presentation

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1595 GENERAL POSTER, SUN, 1:00 PM - 5:00 PM

Pharmacokinetic Features of a Novel 5-HT3-Receptor-Antagonist: Palonosetron (RS-25259–197). *G. Piraccini, R. Stolz, M. Tei, A. Macciocchi; Helsinn Healthcare SA, Pambio-Noranco, Switzerland; GFI Pharmaceuticals, Evansville, IN; University of Tokyo, Dep FBP, Tokyo, Japan*

Palonosetron is a novel, potent, selective 5-HT3-receptor antagonist with high degree of efficacy in animal models (1, 2). It acts by blocking a cascade of neuronal activation and performs its anti-emetic and anti-nausea activity at central and gastrointestinal sites. Therapy with palonosetron is intended for patients receiving emetogenic chemotherapy or undergoing surgical procedures, who need acute or long-lasting anti-emetic coverage. Two phase I dose-ascending clinical trials, performed in US and Japanese subjects, were aimed at assessing the pharmacokinetic properties and the safety profile of palonosetron IV administered in a range of dosages from 0.1 to 90 mcg/kg. A third study was conducted on healthy volunteers in order to determine the metabolic and pharmacokinetic profile of [14C]-palonosetron in plasma and urine. The results of these studies indicate that palonosetron is moderately bound to plasma proteins (62%), is metabolized at hepatic level (50%), and part is found unchanged in urine (42%). A key element of the pharmacokinetic properties of palonosetron is a long elimination half-life ($t_{1/2}$) of over 40 hours (range 24.0–64.2). In general, palonosetron showed linear kinetics. The drug was well tolerated, no dose-related incidence of adverse events (AEs) and no unexpected or serious AEs were recorded. The most common AEs were headache and constipation that were generally mild or moderate. These findings in human volunteers suggest potential therapeutic benefits in terms of potency and longer duration of action with respect to available therapies. References 1. Wong E.H.F. et al., British J Pharm, 114:851–859, 1995. 2. Eglen R.M. et al., British J Pharm, 114:860–866, 1995.

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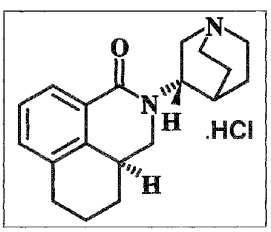
ABSTRACT

Palonosetron is a novel, potent, selective 5-HT_3-receptor antagonist with high degree of efficacy in animal models [1, 2]. It acts by blocking a cascade of neuronal activation and performs its anti-emetic and anti-nausea activity at central and gastrointestinal sites. Therapy with palonosetron is intended for patients receiving emetogenic chemotherapy or undergoing surgical procedures, who need acute or long-lasting anti-emetic coverage. Two phase I dose-ascending clinical trials, performed in US and Japanese subjects, were aimed at assessing the pharmacokinetic properties and the safety profile of palonosetron IV administered in a range of dosages from 0.1 to 90 mcg/Kg. A third study was conducted on healthy volunteers in order to determine the metabolic and pharmacokinetic profile of [^{14}C]-palonosetron in plasma and urine. The results of these studies indicate that palonosetron is moderately bound to plasma proteins (62%), is metabolized at hepatic level (50%), and part is found unchanged in urine (42%). A key element of the pharmacokinetic properties of palonosetron is a long elimination half-life (t ½) of over 40 hours (range 24.0-64.2). In general, palonosetron showed linear kinetics. The drug was well tolerated, no dose-related incidence of adverse events (AEs) and no unexpected or serious AEs were recorded. The most common AEs were headache and constipation that were generally mild or moderate. These findings in human volunteers suggest potential therapeutic benefits in terms of potency and longer duration of action with respect to available therapies.

INTRODUCTION

Palonosetron hydrochloride is a potent selective 5-HT_3-receptor antagonist. Palonosetron prevents activation of the vomiting reflex by blocking the binding of serotonin to the 5-HT_3 receptors in a manner similar to that of ondansetron, granisetron and dolasetron. In pre-clinical studies, palonosetron exhibited significant activity in the prevention of nausea and vomiting induced by both highly and moderately emetogenic chemotherapy [1, 2]. This positive pre-clinical activity of palonosetron warranted further investigation.



Palonosetron hydrochloride (3a<u>S</u>-2-[<u>CS</u>]1-zabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1<u>H</u>-benx1[<u>de</u>]isoquinoline hydrochloride)

M.W.:332.87

[1] Wong E.H.F. et al., *British J Pharm*, 114:851-859, 1995
[2] Eglen R.M. et al., *British J Pharm*, 114:860-866, 1995

MATERIALS AND METHODS

Three phase I studies were performed to assess the safety, tolerat pharmacokinetic, metabolic and excretion profile of palonosetron the studies were randomized, double-blind, placebo-controlled formed in healthy volunteers with administration of single ascer doses of palonosetron **(Study 1 & 2)**. The third study performed o subjects administered [^{14}C]-palonosetron, was carried out in orde acterize the metabolic profile in plasma and urine, the pharma parameters of total radioactivity and the excretion profile of **(Study 3)**.

Study 1: 80 male US subjects were randomized (3:1 ratio) t either study drug or placebo. Palonosetron was administered a lowing doses: 0.3, 1, 3, 10, 20, 30, 45, 60 and 90 mcg/Kg. Study tion was administered by a single 5-minute I.V. infusion.

Study 2: 32 male Japanese subjects were randomized (3:1 receive either study drug or placebo. Palonosetron doses were: and 90 mcg/Kg. Study medication was administered by a single 3(I.V. bolus injection.

In both trials, the higher dose was administered after assessm safety data of the preceding group. Subjects underwent physical e tion, ECG and Holter (study 1) and routine laboratory tests before entering the study. Blood and urine samples were collected for t macokinetic analysis before and after dose administration. remained in the unit for 72 hrs after dosing and the last control performed 1 week later. Adverse events (AEs) were monitored d 72 hrs of the study period and any reports of AEs occurring thereaf captured from patient diary entries.
Among the pharmacokinetic parameters evaluated for palonosetro N-oxide metabolite (M9), the following are reported in tables 2–4

- plasma half-life (t ½),
- time to maximum observed plasma concentration (T_{max}),
- maximum observed plasma concentration (C_{max}),
- area under plasma concentration-time curve from 0 to infi AUC).

The following parameters were calculated only for palonosetron:

- clearance (Cl) and
- volume of distribution ($V_{dβ}$).

Parent and metabolite identification in urine was made only in the est dose groups in study 1 and on all groups in study 2.
Statistical calculations were done using the SAS procedure PRO

Study 3: Three male and three female healthy volunteers were e in an open-label, single-dose, metabolic-disposition study. The were administered a single I.V. dose (10 µg/Kg or 0.8 µCi/Kg) palonosetron. Blood and urine samples were taken before and a ing. AEs were collected during the whole observation period (11 The following pharmacokinetic parameters were evaluated:

- total radioactivity in all blood samples for palonosetro metabolites
- total radioactivity in all urine samples for palonosetron and lites
- the metabolic profile in plasma and urine,
- qualitative tests for β-glucuronide and sulfate conjugates in structural characterization of the metabolites in urine.

The calculated pharmacokinetic parameters were T_{max}, C_{max}, t ½, plasma ratio for total radioactivity, $AUC_{0\text{-}96}$, $AUC_{0\text{-last}}$, AUC0-∞, V t ½, total radioactivity in urine to last measurable Au (A_u 0-las radioactivity in urine from last measurable Au to infinity (A_u last t-∞ lative radioactivity (Au 0-) and renal clearance (Cl_r).
All adverse events were followed until the overall clinical outc ascertained.

tures of a Novel 5-HT$_3$-Receptor-Antagonist: Palon

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unetetsu Tei, School of Medicine, University of Tokyo, (Tokyo, Japan); and Alberto Macciocchi, Helsinn Healthcare SA, (Lugano, Switzerland)

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Variable	Study 1 N=80	Study 2 N=32	Study 3 N=6
AGE (years)	26 6	22 7	35
WEIGHT (Kg)	80	63 3	75
HEIGHT (cm)	178 4	171 8	174
RACE			
Asian	3 8%	100%	0%
Black	6 3%	0%	17%
Caucasian	90 0%	0	83%

Table 1 Demographic data of subjects enrolled in studies 1 2 and 3

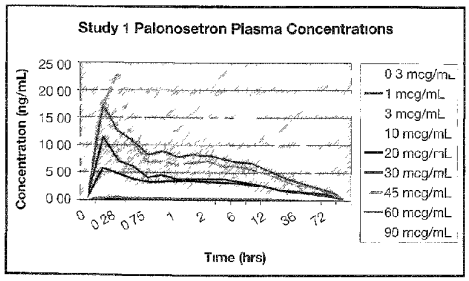
RES

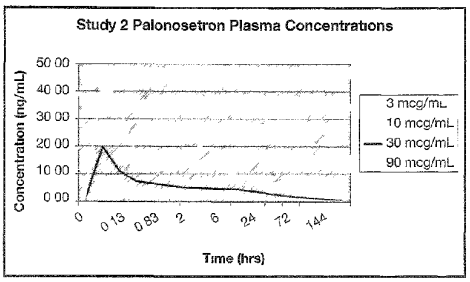
Variable	0 3 mcg/Kg n=6	10 mcg/Kg n=6	3
C_{MAX} (ng/mL)			
Palonosetron	4 68±4 68	7 79±3 31	2
N-Oxide (M9)	0 0933±0 0545	0 170±0 0669	0
T_{MAX} (hr)			
Palonosetron	0 692±1 62	0 0167±0	0
N-Oxide (M9)	42 7±67	6 67±4 33	3
HALF-LIFE (hr)			
Palonosetron	30 8±9 22	34 1±3 75	3
N-Oxide (M9)	nc	37 4±19 2	2
TOTAL AUC (ng hr/mL)			
Palonosetron	15 2±4 58	51 2±9 44	
N-Oxide (M9)	nc	6 70±2 76	
CLEARANCE (mL/min/Kg)	3 50±0 817	3 37±0 747	2
VOLUME OF DISTRIBUTION (L/Kg)	8 81±1 38	9 85±1 90	(

Table 3 Pharmacokinetic data of palonosetron and its metabolite (M9) fr

Variable	0 3 mcg/Kg n=6	1 mcg/Kg n=6	3 mcg/Kg n=6	10 mcg/Kg n=12	20 mcg/Kg n=6	30 mcg/Kg n=6	45
C_{MAX} (ng/mL)							
Palonosetron	0 114±0 063	0 349±0 206	0 918±0 250	3 53±1 44	5 71±2 93	11 5±8 71	2(
N-Oxide (M9)	0	0	0	0 102±0 0183	0 156±0 0414	0 443±0 201	0 4
T_{MAX} (hr)							
Palonosetron	0 736±1 60	0 825±1 56	0 0833±0 00	0 0903±0 0241	0 556±0 732	0 403±0 782	0 3
N-Oxide (M9)TMAX (hr)	0	0	0	3 67±1 51	6 00±1 26	5 33±2 42	5
HALF-LIFE (hr)							
Palonosetron	54 1±36 6	33 7±16 8	47 2±14 7	35 0±8 77	37 0±6 15	37 8±6 60	4
N Oxide (M9)	0	0	0	0	19 6±0 394	19 3±15 4	5
TOTAL AUC (ng hr/mL)							
Palonosetron	5 80±3 46	9 35±2 59	29 8±9 02	65 7±14 5	153±44 1	150±56 1	3
N-Oxide (M9)	0	0	0	0	5 51±1 29	10 3±4 47	2
CLEARANCE (mL/min/Kg)	1 11±0 652	1 89±0 456	1 81±0 547	2 66±0 805	2 36±0 766	3 90±1 81	2
VOLUME OF DISTRIBUTION (L/Kg)	3 85±0 645	5 31±2 35	6 88±0 874	7 83±1 81	7 27±1 19	12 6±5 52	8

Table 2 Pharmacokinetic data of palonosetron and its metabolite (M9) from subjects of study 1 (mean ±SD)





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