American Society of Clinical Oncology (ASCO) May 12-15, 2001 San Francisco - USA

- <u>Reference</u>: Program/Proceedings American Society of Clinical Oncology, Vol. 20, Part 1 of 2, 2001 Abstract no. 1595
- **<u>Topic</u>**: phase I trials, pk and safety, i.v. administration
- <u>Note</u>: abstract and poster presentation

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Dr. Reddy's Laboratories, Ltd., et al.

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Symptom Management

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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 antinausea 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.



Pharmacokinetic Featur

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ABSTRACT

Palonosetron is a novel, potent, selective 5-HT₃-receptor antagonist with high degree of efficacy in animal models (). 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 longlasting 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.

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.



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

MW-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 or subjects administered ["C]-palonosetron, was carried out in order 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) tr 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 assessme safety data of the preceding group. Subjects underwent physical e tion, ECG and Holter (study 1) and routine laboratory tests beforeentering 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 thereai captured from patient diary entries.

Among the pharmacokinetic parameters evaluated for palonosetre N-oxide metabolite (M9), the following are reported in tables 2–4 – plasma half-life (t ½).

- time to maximum observed plasma concentration (Tmax),
- maximum observed plasma concentration (C_{max}),
- area under plasma concentration-time curve from 0 to infir, AUC).

The following parameters were calculated only for palonosetron: - clearance (CI) and

volume of distribution (V_{dβ}).

Parent and metabolite identification in urine was made only in the ⁶ 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 ε in an open-label, single-dose, metabolic-disposition study. The were administered a single I.V. dose (10 µg/Kg or 0.8 µCl/Kg) palonosetron. Blood and urine samples were taken before and a ing. AEs were collected during the whole observation period (11 c The following pharmacokinetic parameters were evaluated:

- total radioactivity in all blood samples for palonosetrol 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 ι structural characterization of the metabolites in urine,

The calculated pharmacokinetic parameters were $T_{viax}, C_{mex}, t \frac{1}{2}$, plasma ratio for total radioactivity, AUCO-ee, AUCO-ee, AUCO-ee, AUCO-ee, t $\frac{1}{2}$, total radioactivity in urine to last measurable Au (A_u O-las radioactivity in urine from last measurable Au to infinity (A_u last t-e lative radioactivity (Au 0-) and renal clearance (Clr).

All adverse events were followed until the overall clinical outco ascertained.

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tures of a Novel 5-HT₃-Receptor-Antagonist: Palon

Gaia Piraccini*, Helsinn Healthcare SA, (Lugano, Switzerland), Randall Stolz, GFI Pharmaceutical Services, (Evansville, IN - USA); unetetsu Tei, School of Medicine, University of Tokyo, (Tokyo, Japan); and Alberto Macciocchi, Helsinn Healthcare SA, (Lugano, Switzerland)

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ety, tolerability, and prosetron Two of	Variable	Study 1 N=80	Study 2 N=32	Study 3 N=6	Variable	0 3 mcg n=6	ı/Kg 1	10 mcg/Kg n=6	
gle ascending I V rformed on healthy ut in order to char-	AGE 26 6 (years)		22 7	35	C _{MAX} (ng/mL) Palonosetron N-Oxide (M9)	4 68±4 68 0 0933±0 0545		7 79±3 31 170±0 0669	2 0
rofile of the drug	WEIGHT 80 (Kg)		63 3	75	T _{MAX} (hr) Palonosetron N-Oxide (M9)	0 692± 42 7+(1 62 0 C	0 0167±0 6 67+4 33	
nistered at the fol- Kg Study medica-	HEIGHT (cm)	178 4	171 8	174	HALF-LIFE (hr) Palonosetron	30 8±9	3 22	34 1±3 75	
ized (3 1 ratio) to es were 3, 10, 30 a single 30-second	RACE Asian Black Caucasian	3 8% 6 3% 90 0%	100% 0% 0	0% 17% 83%	TOTAL AUC (ng Palonosetron N-Oxide (M9) CLEARANCE (ml	hr/mL) 15 2±4 nc L/min/Kg) 3 50±(4 58 0 817	51 2±9 44 6 70±2 76 3 37±0 747	
assessment of all physical examina- its before and after socied for the phar- tration Subjects st control visit was	Table 1 Demographic data of subjects enrolled in studies 1 2 and 3 Volume OF Distribution (L/Kg) 8 81±1 38 9 85±1 90 Table 3 Pharmacokanetic data of palonosetron and its metabolite (
ing thereafter were	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
alonosetron and its ables 2–4	C _{MAX} (ng/mL) Palonosetron N-Oxide (M9)		0 114±0 063 0	0 349±0 206 0	0 918±0 250 0	3 53±1 44 0 102±0 0183	5 71±2 93 0 156±0 0414	11 5±8 71 0 443±0 201	2(0 4
1 0 to infinity (total	T _{MAX} (hr) Palonosetron N-Oxide (M9)T	MAX (hr)	0 736±1 60 0	0 825±1 56 0	0 0833±0 00 0	0 0903±0 0241 3 67±1 51	0 556±0 732 6 00±1 26	0 403±0 782 5 33±2 42	035
nosetron	HALF-LIFE (hr) Palonosetron N Oxide (M9)		54 1±36 6 0	33 7±16 8 0	47 2±14 7 0	35 0±8 77 0	37 0±6 15 19 6±0 394	37 8±6 60 19 3±15 4	4 5,
nly in the two high dure PROC GLM	TOTAL AUC (ng hr/mL) Palonosetron N-Oxide (M9)		5 80±3 46 0	9 35±2 59 0	29 8±9 02 0	65 7±14 5 0	153±44 1 5 51±1 29	150±56 1 10 3±4 47	3 2
ars were evaluated udy The subjects 8 uCi/Kg) of [*C]	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
ore and after dos eriod (11 days)	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
lonosetron and/or	Table 2 Pharm	acokinetic dati	a of palonosetron	and its metaboli	ite (M9) from sub	jects of study 1 (m	iean ±SD)		
etron and metabo			-			- · ·			

ugates in urine and ine C_{max} t ½ blood to \UCO-∞ V_{dµ} urine (A_u 0-last t) total Concentration (ng/mL)

Aulast t-∞) cumu lical outcome was

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Study 1 Palonosetron Plasma Concentrations 25 00 0.3 mcg/m⊾ 20 00 •1 mcg/mL 3 mcg/mL 15 00 10 mcg/mL 10.00 20 mcg/mL 5 00 -30 mcg/mL ~45 mcg/mL 0.00 60 mcg/mL 0 028 075 ٩ 2 6 12 36 12 90 mcg/mL Time (hrs)



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