REVIEW ARTICLE

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Zanamivir
A Review of Clinical Safety

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Abstract

Preclinical and clinical studies have clearly demonstrated that zanamivir, a potent and highly selective inhibitor of the influenza A and B virus neuraminidase, has an impressive safety profile.

This report describes the safety and tolerability findings from the clinical studies completed up to the 17 July 1998 involving over 6000 adult and adolescent patients from North America, Europe and the Southern Hemisphere. Serious adverse events from an ongoing Japanese clinical programme are also reported. Zanamivir was administered in various dose forms and frequencies and was found to have a comparable safety profile with placebo when given for both the treatment and prophylaxis of influenza-like illness. These findings were independent of age and underlying medical condition. 4152 patients received zanamivir and

the most commonly reported adverse events were consistent with the signs and symptoms of influenza-like illness. Most of the adverse events were mild and did not result in patient withdrawal from the studies. Less than 1% of zanamivir and placebo recipients reported a serious adverse event.

In addition, 490 healthy volunteers received zanamivir in clinical pharmacology studies. It was well tolerated and the incidence of adverse events was similar in zanamivir and placebo recipients. In addition, no clinically significant laboratory abnormalities were detected.

Results from *in vitro* and *in vivo* animal studies suggest that zanamivir has low acute toxicity and no significant systemic toxicity or respiratory tract irritancy at plasma exposures more than 100-fold higher than those anticipated following clinical use. Neither genotoxic nor reproductive types of toxicity have been observed in toxicology studies at doses equal to 17 to 197 times the current therapeutic dose (20 mg/day). The characteristics of the molecule and the low systemic exposure indicate a very low potential for drug interactions with the inhaled route. Furthermore, repeated 600mg intravenous doses were well tolerated in healthy volunteers.

The observed safety profile of zanamivir compares favourably with currently available agents with anti-influenza virus activity, such as rimantadine and amantadine, as well as GS4104, a neuraminidase inhibitor currently in phase III development. This may be attributed to the low systemic bioavailability of zanamivir, which is given by oral inhalation, direct to the primary site of viral replication. The potential advantages of this include a reduced risk of drug-drug interactions, other nontarget organ toxicities (e.g. brain) and drug clearance issues from both kidney and liver. Therefore, the safety profile of zanamivir supports its use in the management of influenza.

Outbreaks of influenza occur annually, usually in the winter months. Influenza infection is primarily spread by small droplets. After a short incubation period, there may be rapid onset of fever and symptoms which may include chills, myalgia, headache, sore throat, malaise, anorexia and cough. The fever may last for up to 5 days and the other symptoms, with the exception of cough and malaise which may persist, usually resolve within a week.[1] Mortality is highest in the very young and elderly populations with underlying medical conditions such as chronic respiratory and cardiovascular disease.[2]

Currently, the management of influenza is primarily by symptomatic therapy with antipyretics, analgesics and cough suppressants, and prophylaxis, in the form of preseason immunisation with inactivated vaccine. Antiviral drugs are still not widely prescribed for influenza. Amantadine and rimantadine are available in some countries for the treatment and/or prophylaxis of influenza A only. However, they are ineffective against influenza B and are associated with rapid emergence of resistant virus.[3] Moreover, amantadine administered for prolonged periods is associated with a clinically important, increased incidence of adverse effects compared with placebo and rimantadine.[4]

Zanamivir is a potent and highly selective inhibitor of the influenza A and B virus neuraminidase. The activity of zanamivir *in vitro* and *in vivo* is similar for influenza A and influenza B viruses.[5] The drug is active in animal models when administered topically to the respiratory epithelium by inhalation.[6] It has also demonstrated efficacy in both the treatment and prophylaxis of influenza following intranasal administration to adults experimentally inoculated with influenza A and B virus.[7,8] In clinical studies, zanamivir has proved to

be effective in the treatment of influenza A and B viral infections, when given within 2 days of symptom onset, with a reduction in the median time to alleviation of symptoms of up to 2.5 days.[9,10] Zanamivir has also been evaluated as prophylaxis in the community setting.[11]

This report presents a review of the safety data from the toxicology, clinical pharmacology and clinical studies (phase II and III) completed up to 17 July 1998 in the North American, European and Southern Hemisphere programmes. In addition, serious adverse events reported in a separate Japanese programme are presented. No serious adverse events were reported in a recently published phase II study conducted in Japan.[12]

1. Toxicology

Zanamivir has exceptionally low cytotoxicity to a range of cell types *in vitro*, including cells from explants of human respiratory epithelium.[13] As well as demonstrating high affinity inhibition of influenza virus sialidase (neuraminidase), zanamivir is highly selective for influenza A and B. Its affinity for human placental lysosomal sialidase is approximately 1 million-fold lower than is observed with influenza virus resulting in a high therapeutic index.[13]

The rat and dog were used for most of the *in vivo* toxicology studies as the metabolism of zanamivir in these animals showed very good correlation with metabolism of the drug in humans. The inhaled route was used for the majority of the toxicity studies; these were designed to ensure adequate exposure to the whole respiratory tract and doses of 17 to 197 times the anticipated clinical dose were evaluated.

In order to fully assess the toxicity of zanamivir, studies were also conducted using the intravenous (IV) route to maximise the systemic exposure; plasma concentrations of up to 1336-fold those achieved in clinical use were evaluated. However, clinical experience indicates that the amount of zanamivir within the systemic circulation following inhalation is likely to be low. Nevertheless, the systemic route was chosen to investigate target-organ toxicity, effects on fertility, general reproductive performance and pre- and postnatal development.

The comprehensive toxicology programme, evaluating both the inhaled and IV routes of administration, demonstrated that zanamivir has low acute toxicity, is well tolerated following repeat dosage and exhibits no clinically relevant effects in the animal species studied despite very high systemic exposure.[14]

2. Clinical Pharmacology

The core clinical pharmacology programme consisted of single and repeat-dose IV studies, single oral dose studies and repeated intranasal and inhaled dose studies. All of these studies were conducted in healthy volunteers. Safety and tolerability were assessed by monitoring adverse events throughout the studies; this included performing routine clinical chemistry, haematology and urinalysis before and after each treatment phase plus 7 to 14 days post-treatment, and measuring vital signs (including systolic and diastolic blood pressure, pulse rate, peak expiratory flow rate and respiratory rate) at predetermined times throughout the studies.

In addition, a series of volunteer challenge studies were conducted to evaluate the safety and efficacy of intranasal zanamivir when given 6 times, twice or once daily for the prevention or treatment of experimental influenza infection. One study evaluated zanamivir given intravenously for the prevention of experimental influenza. A single vaccine interaction study was also conducted to assess whether coadministration of zanamivir and inactivated trivalent influenza vaccine (Fluvirin™) affected antihaemagglutinin antibody production (see section 5.2) and a paediatric pharmacokinetic study was conducted using inhaled zanamivir (see section 4.4).

A total of 654 patients participated in the clinical pharmacology programme; 490 received zanamivir and 256 received placebo. Patients were relatively young (mean age 25.31 years for zanamivir and 26.71 for placebo), and the majority were males (62% for zanamivir and 73% for placebo)

and caucasian (84% for zanamivir and 83% for placebo). Zanamivir was well tolerated in all studies with a safety profile similar to placebo.

2.1 Adverse Events

The incidence of adverse events was similar across both treatment groups with 66% of patients who received zanamivir and 68% of patients who received placebo reporting an adverse event. In the core clinical pharmacology studies, 46% of patients who received zanamivir and 46% of patients who received placebo reported adverse events. Headache was the most common adverse event and was reported by 17% of patients in both treatment groups. A total of 23% of patients in each treatment group reported an adverse event that was considered to be possibly related to the study treatment or had an unknown relationship.

Zanamivir administered by all routes as single or repeat doses, was well tolerated at doses of up to 1200 mg/day given by the IV route and 96 mg/day by the inhaled route.

In the challenge studies, 86% of patients who received zanamivir and 94% of patients who received placebo reported adverse events. The most commonly reported adverse events were ear signs and symptoms (45 and 59% of zanamivir and placebo patients, respectively), nasal signs and symptoms (11 and 19% of zanamivir and placebo patients, respectively) and malaise and fatigue (41 and 55% of zanamivir and placebo patients, respectively). A total of 52% of patients who received zanamivir and 60% of patients who received placebo reported treatment-related adverse events.

There were no serious adverse events reported in the clinical pharmacology studies.

There were no clinically significant changes in laboratory parameters. Small increases (not exceeding approximately twice the upper limit of normal) were seen in the liver function tests (LFTs) and for creatine phosphokinase levels for some patients following administration of both placebo and zanamivir; for zanamivir there was no relationship to dose.

No clinically significant effects were observed in vital signs, including spirometry and electrocardiograms.

3. Phase II and III Clinical Studies

The clinical programme consisted of a small number of early pilot studies followed by the main phase II and III studies. Zanamivir was evaluated for 2 indications: treatment of influenza-like illness and prevention of influenza (prophylaxis).

Four pilot studies involving small numbers of patients were conducted with study treatment administered as nasal drops, nasal spray or via a nebuliser (2 treatment studies and 2 prophylaxis studies). A fifth pilot study (prophylaxis) was conducted in a nursing home with zanamivir administered via the Diskhaler™ compared with standard care (rimantadine for influenza A or no treatment for influenza B).

In the main clinical programme, treatment studies were designed to evaluate the efficacy and safety of zanamivir in the treatment of influenza-like illness, and prophylaxis studies were designed to evaluate the prophylactic effect and safety of zanamivir in patients who had been exposed to the influenza virus. The phase II programme utilised the Diskhaler™ device for oral inhalation and a nasal spray. The study treatment was administered via the Diskhaler™ by oral inhalation in all the phase III studies.

Safety and tolerability were assessed by monitoring adverse events throughout all studies. These were recorded following spontaneous reporting by patients and direct questioning by the investigator. At each visit, after the patient had an opportunity to spontaneously mention any problems, the investigator was asked to inquire about adverse events. The patients were not given a list of possible adverse effects but were asked about any problems they may have experienced. In addition, blood and urine samples for routine clinical chemistry, haematology and urinalysis were collected immediately before and after the treatment period and at follow-up (approximately 2 weeks later) in the early pilot and phase II studies. Physical examina-

tions pre- and post-treatment, if clinically indicated, were also conducted in the early pilot and phase II/III studies.

3.1 Treatment Indication

A total of 3809 patients received study treatment; the majority of patients were healthy adults (79% were aged 18 to 34 years) with 119 (3%) aged ≥65 years of age. 2289 (60%) received zanamivir, 49% of whom were treated with zanamivir 10mg twice daily via the Diskhaler™ for 5 days, the dose form and regimen intended for marketing. The remaining 51% of patients received doses of zanamivir in excess of this either with additional nasal administration or at an increased frequency of daily doses. The mean age of patients was 34.2 years with 51% being female; the majority (91%) of patients were caucasian. Overall, patients were well matched across all the treatment studies for age, gender distribution and race.

3.1.1 Adverse Events

The proportion of patients who reported adverse events during treatment was similar in the zanamivir group (33%) and placebo group (38%). The most commonly reported adverse events (i.e. reported in ≥1.5% patients) are presented in table I.

Post-treatment adverse events were reported by 24% of patients in both the zanamivir and placebo groups. Headache was the most common adverse event and was reported by 4% of patients in the zanamivir group and 3% of patients in the placebo group.

The incidence of drug-related adverse events during treatment was similar between the treatment groups, occurring in 13% of zanamivir and 11% of placebo recipients. Only 2% of patients in each treatment group reported drug-related adverse events post-treatment.

3.1.2 Clinical Laboratory Data

Threshold values were predetermined for each parameter. No clinically significant differences between treatment groups were observed. Shifts from baseline to outside threshold range occurred in ≥1.5% patients for the parameters detailed in table II.

The changes observed were considered likely to be due to the influenza-like illness or other concurrent medical condition. Laboratory changes over time were similar between the zanamivir and placebo treatment groups.

3.2 Prophylaxis Indication

A total of 1808 patients received study treatment, 1063 (59%) of whom received zanamivir.

Table I. Treatment indication: summary of most common adverse events (during treatment)

Adverse effect	Number of patients reporting an event (%)		
	placebo (n = 1520)	zanamivir 10mg bid inhaled (n = 1132)	zanamivir: all regimens (n = 2289)
Nasal signs and symptoms	44 (3)	20 (2)	62 (3)
Diarrhoea	55 (4)	29 (3)	64 (3)
Nausea	44 (3)	32 (3)	70 (3)
Headache	40 (3)	20 (2)	52 (2)
Bronchitis	52 (3)	28 (2)	39 (2)
Cough	42 (3)	27 (2)	42 (2)
Sinusitis	27 (2)	30 (3)	42 (2)
Throat and tonsil discomfort	19 (1)	15 (1)	33 (1)
Vomiting	29 (2)	14 (1)	24 (1)
Dizziness	12 (<1)	18 (2)	32 (1)
Ear, nose and throat infection	25 (2)	17 (2)	31 (1)
Ear, nose and throat haemorrhage[a]	18 (1)	16 (1)	32 (1)

a Includes adverse events reported as epistaxis by the investigator.

bid = twice daily.

Table II. Treatment indication: summary of changes in laboratory values from baseline to a value outside threshold range (incidence ≥1.5%)

Measure	Change category	Placebo (% of patients) [n = 1520]	Zanamivir (% of patients) [n = 2289]
Bicarbonate level	to >1.05 ULN	4	4
Calcium level	to <0.95 LLN	2	1
γ-glutamyl transferase level	to >2.00 ULN	6	3
Glucose level	to >1.30 ULN	3	3
Potassium level	to >1.10 ULN	2	3
AST level	to >2.00 ULN	2	2
ALT level	to >2.00 ULN	3	3
Haematocrit	to <0.93 male/0.91 female LLN	2	1
Neutrophils count	to <0.80 LLN	9	8
White blood cell count	to <0.70 LLN	2	<1

LLN = lower limit normal; **ULN** = upper limit normal.

Various dose regimens were evaluated in the early studies; however, the majority (52%) of patients received zanamivir 10mg once daily for 28 days via the Diskhaler™. The mean age of patients was 30.6 years with 59% of patients being female; the majority of patients were caucasian (86%). Overall, patients were well matched for age, gender distribution and race across all the prophylaxis studies.

3.2.1 Adverse Events

The proportion of patients who reported adverse events during therapy was the same in both the zanamivir and placebo groups (71%). The most commonly reported adverse events during therapy (i.e. reported in ≥1.5% patients) are presented in table III.

Post-therapy adverse events were reported by 26% of patients in the zanamivir group and 23% of patients in the placebo group. Headache was the most common adverse event and was reported by 6% of patients in both the zanamivir and placebo groups. Nasal signs and symptoms were reported by 5% of patients in the zanamivir group and 6% of patients in the placebo group.

The incidence of treatment-related adverse events reported during therapy was similar between treatment groups occurring in 11% of zanamivir and 8% of placebo recipients. Only 3% patients in the zanamivir group and 1% of patients in the placebo group reported adverse events post-therapy.

The overall percentage of adverse events reported in the prophylaxis studies for both the placebo and zanamivir treatment groups were higher than that observed in the other studies.

In the prevention studies, 60% of patients were recruited from an essentially healthy young population (mean age 30.6 years), from whom any symptom reported over this time (1 month) was recorded as an adverse event. Conversely, in the treatment studies on therapy, adverse events were only collected for 5 days and, importantly, any event considered as part of the influenza-like illness (e.g. headache, cough, myalgia) was not recorded as an adverse event. This explains the apparent disparity in reported adverse events; it is relevant to note that the comparative rate of adverse events between zanamivir and placebo was not different within each study type.

Overall, in the prophylaxis studies the nature and incidence of adverse events was similar between zanamivir and placebo groups. The most commonly reported adverse events (reported at an incidence of 1.5 to 41%) were typical of the signs and symptoms of respiratory viral infection and gastrointestinal events, i.e. headaches, nasal signs and symptoms, throat and tonsil discomfort and pain, malaise and fatigue, cough, nausea and diarrhoea, and were similar to those observed in the treatment studies.

3.2.2 Clinical Laboratory Data

Threshold values were predetermined for each parameter. No clinically significant differences between treatment groups were observed. Shifts from baseline to outside threshold range occurred in ≥1.5% patients for the parameters detailed in table IV. Laboratory changes over time were similar between the zanamivir and placebo treatment groups.

3.3 Clinical Pilot Studies

Early pilot studies, which generally did not fully recruit, consisted of 2 treatment studies and 2 prophylaxis studies, all conducted in healthy adults (mean age 29.9 years), and 1 prophylaxis study in elderly patients in a nursing home setting (mean age was 73.8 years).

In these 5 trials, 188 patients received placebo or no treatment and 310 received at least 1 dose of zanamivir with a minimum of 12.8mg intranasal and/or 16mg inhaled zanamivir in the pilot studies and 6.4mg intranasal and 10mg inhaled in the pilot nursing home study. The pilot nursing home study also had an oral rimantadine 100mg once daily arm comprised of 23 patients.

3.4 Deaths and Nonfatal Serious Adverse Events

Two deaths have been reported in clinical trials to date, both of which have occurred during an ongoing prophylaxis study being conducted in a nursing home. Both patients were elderly (aged 82 and 83 years) and the investigator did not consider either event to be related to study medication. One patient was receiving placebo and rimantadine 100mg once daily and the second patient was receiving zanamivir 10mg inhaled once daily.

A total of 62 patients have reported serious adverse events in the clinical studies (including all ongoing studies and 4 serious adverse events reported in a separate Japanese programme); 47 reports are from completed studies. Of these, 28 of 3662 (<1%) patients received zanamivir, 18 of 2436 (<1%) patients received placebo and 1 of 23 (4%) patients received rimantadine. Four patients experienced a serious adverse event that was considered by the investigator to be possibly related to study medication; 3 patients received placebo and 1 had received zanamivir (frontal headache, dizziness and nasal pain). The nature and frequency of

Table III. Prophylaxis indication: summary of most common adverse events (during therapy)

Adverse effect	Number of patients reporting an event (%)		
	placebo (n = 745)	zanamivir: 10mg inhaled (n = 744)	zanamivir: all regimens (n = 1063)
Headache	309 (41)	302 (41)	393 (37)
Nasal signs and symptoms	269 (36)	265 (36)	349 (33)
Throat and tonsil discomfort	231 (31)	224 (30)	269 (25)
Malaise and fatigue	182 (24)	180 (24)	228 (21)
Cough	180 (24)	160 (22)	192 (18)
Temperature regulation disturbances[a]	115 (15)	88 (12)	106 (10)
Feeding problems[b]	101 (14)	80 (11)	87 (8)
Muscle pain	77 (10)	79 (11)	113 (11)
Musculoskeletal pain	85 (11)	67 (9)	71 (7)
Viral respiratory infections	27 (4)	20 (3)	59 (6)
Menstrual symptoms	27 (4)	24 (3)	26 (2)
Nausea	20 (3)	20 (3)	24 (2)
Diarrhoea	18 (2)	9 (1)	14 (1)
Eye pain and discomfort	17 (2)	12 (2)	12 (1)
Eye redness	15 (2)	10 (1)	10 (<1)
Sputum	14 (2)	11 (1)	11 (1)

a Includes adverse events reported as fever by the investigator.

b Includes adverse events reported as loss of appetite by the investigator.

the serious adverse events reveal no pattern and raise no particular safety concerns.

4. Special Patient Groups

4.1 Patients with Mild to Moderate Asthma

A clinical pharmacology study involving 13 patients with mild to moderate asthma was conducted to evaluate the effect of repeat doses of inhaled zanamivir on pulmonary function and bronchial hyper-responsiveness.[15] Mild to moderate asthma was defined as having a history of asthma for >2 years, a forced expiratory volume in 1 second (FEV_1) of >70% predicted, provocative dose of methacholine to produce a 20% fall in forced expiratory volume in 1 second (PD_{20}) methacholine at screening of <4 μmol/L and reversibility of FEV_1 of >15% after salbutamol 200μg. The study was conducted with a double-blind, randomised, placebo-controlled, 2-way crossover design. Patients received zanamivir as dry powder (10mg as 2 inhalations) or matching placebo twice daily on day 1 and then 4 times daily from day 2 to day 14.

The study treatments were well tolerated by all patients with no clinically significant abnormalities attributable to zanamivir. Results indicated that inhalation of dry powder zanamivir does not significantly affect the pulmonary function [measured by FEV_1 and morning and evening peak expiratory flow rate (PEFR)] and bronchial hyper-responsiveness [assessed by comparison of the concentration of methacholine that caused a 20% decrease in FEV_1 (PC_{20}) as recorded during the methacholine challenge tests which were conducted prestudy and at regular intervals on days 1 and 14] of patients with mild/moderate asthma.

A total of 129 adverse events were reported by the 13 patients during the study. Most adverse events resolved completely and those that remained were either related to the patients' asthma or to a response to seasonal allergens (such as hayfever). 37 adverse events (23 events in 7 placebo recipients and 14 events in 6 zanamivir recipients) were considered related to study treatment. These were headaches (4 placebo recipients, 3 zanamivir recipients), tight chest (4 placebo, 1 zanamivir recipient), wheezing (3 placebo, 1 zanamivir recipient), increased breathlessness (1 placebo, 1 zanamivir recipient), low FEV_1 (1 placebo recipient), malaise and fatigue (1 placebo recipient), dizziness (1 placebo recipient), throat and tonsil discomfort (1 placebo recipient), abnormal LFTs (1 placebo recipient) and nausea and vomiting (1 zanamivir recipient). No serious adverse events were reported.

These observations suggest that the use of orally inhaled dry powder zanamivir should not be precluded in patients with asthma.

In addition, 271 patients with chronic respiratory disease and influenza-like illness were enrolled in the phase II and III clinical studies; the majority of these were diagnosed as having asthma. Adverse events were reported during treatment by 39% of patients in the zanamivir group compared with 48% of patients in the placebo group. The most frequently reported adverse event was exacerbation of asthma (7% zanamivir, 15% placebo). This was in keeping with the expected clinical course of acute influenza in patients with pre-existing asthma or reactive airways disease.

Table IV. Prophylaxis indication: summary of changes in laboratory values from baseline to a value outside threshold range

Measure	Change category	Placebo (%)	Zanamivir (%)
Bicarbonate level	to >1.05 ULN	1	2
	to <0.95 LLN	5	4
γ-glutamyl transferase level	to >2.00 ULN	2	1
Glucose level	to >1.30 ULN	2	3
ALT level	to >2.00 ULN	1	2
Lymphocyte count	to <0.80 LLN	2	2

LLN = lower limit normal; **ULN** = upper limit normal.

4.2 Patients with Renal Impairment

As systemically absorbed zanamivir is eliminated by urinary excretion, there is the potential for renal impairment to influence its elimination. This was assessed by comparing the pharmacokinetics of zanamivir following a single IV infusion with zanamivir in 17 patients with renal function ranging from normal to severe renal failure (4mg to patients who were healthy or had mild to moderate renal impairment, 2mg to patients with severe renal impairment).

The study demonstrated that zanamivir was well tolerated in both healthy patients and those with renal impairment.[16] In patients with renal impairment, there was a linear correlation between reduced creatinine clearance and an increase in serum zanamivir concentrations resulting in increased systemic exposure in these patients. However, at the proposed therapeutic daily dose of 20mg inhaled zanamivir, absolute bioavailability is low (approximately 10%) and there is limited systemic absorption; therefore, the increased exposure in patients who are renally-impaired is not considered to be a problem. Also, there is no accumulation or toxicity with high serum concentrations of zanamivir. Zanamivir was well tolerated in healthy patients who received far higher systemic doses (IV zanamivir 600mg twice daily for 5 days); therefore, a reduction in the therapeutic dose is not warranted for patients with renal impairment.

A total of 9 adverse events were reported by 5 patients during the study. Two adverse events were considered to be possibly treatment-related (moderate headache and mild soreness at the cannula site). All 9 adverse events resolved completely. There were no serious adverse events. Several potentially clinically relevant deviations in the clinical chemistry and haematology screens were noted for 12 patients. However, in each case these were associated with the patient's pre-existing medical condition and there were no exacerbations following treatment with zanamivir. There were no clinically relevant deviations in the urinalysis.

4.3 Elderly Patients

The safety and tolerability of zanamivir in elderly patients have not been specifically studied in either the clinical pharmacology or clinical programmes. However, elderly patients aged 65 and above were recruited in the later phase II and phase III treatment and prophylaxis studies. As only a small fraction of the inhaled zanamivir dose is absorbed systemically and higher systemic concentrations were well tolerated in younger adults, any alteration in pharmacokinetics that may occur with age is unlikely to be of clinical consequence. In addition, the local concentrations achieved in the lung following oral inhalation of zanamivir are required for efficacy and, therefore, no dose adjustment is considered appropriate.

A total of 119 elderly patients participated in the phase III treatment studies of whom 59 received zanamivir. The pattern and incidence of adverse events was similar across treatment groups (zanamivir 43%, placebo 39%) and events most commonly involved the lower respiratory tract and gastrointestinal tract.

A randomised, unblinded, pilot, prophylaxis study was conducted in individual nursing homes units during influenza outbreaks.[17] 14 days' treatment with zanamivir (10mg orally inhaled plus 4.4mg intranasally, twice daily) was compared with standard care. 85% of the patients recruited were aged 65 years or older. A total of 98 patients received zanamivir, 23 received rimantadine (100mg once daily for influenza A) and 18 received no antiviral drug treatment.

During therapy, adverse events were reported by 39% of patients who received zanamivir, 35% of patients who received rimantadine and 59% who received no antiviral treatment. Nasal signs and symptoms were the most common adverse event and these were reported by 11% of patients who received zanamivir. The only post-therapy adverse events reported by 5 or more patients in any group were chest sounds on auscultation which were reported by 5% of patients who received zanamivir, 9% of patients who received rimantadine and 12% of patients who received no treatment. Only one

serious adverse event was reported in a patient who received rimantadine. The incidence of treatment-related adverse events reported during therapy was similar between treatment groups. 40 of the patients had pre-existing mild to severe chronic obstructive pulmonary disease and no differences in the number or severity of adverse events was observed in this group when compared with the zanamivir group.

Shifts from baseline to a value outside the threshold range were seen in 5 or more patients for the following parameters: glucose (16% of zanamivir patients, 13% of rimantadine patients and 16% on no antiviral therapy), blood urea (8% of zanamivir patients, 22% of rimantadine patients) and haemoglobin (6% of zanamivir patients, 17% of rimantadine patients and 6% on no antiviral therapy).

4.4 Paediatric Patients

In the paediatric pharmacokinetic study, 24 patients aged between 3 months and 12 years received a single dose of inhaled zanamivir 10mg administered by nebuliser (patients aged 3 months to 4 years) or Diskhaler™ (patients aged 5 to 12 years). The systemic exposure in these paediatric patients was found to be similar to the systemic exposure in adults after 10mg inhaled powder via the Diskhaler™. The rate and extent of absorption were similar irrespective of inhalation formulation or the age of the patient. Urinary data showed less than 8% of the drug to be excreted unchanged in the urine within 8 hours of inhalation, confirming a low bioavailability.

Zanamivir was well tolerated with 6 patients experiencing a total of 7 adverse events (Peng AW, et al., unpublished observations). All of the events were considered mild and nonserious. One event, a headache in a 12-year-old girl, was thought to be possibly related to zanamivir.

The studies completed in the clinical programme recruited patients aged 12 years and older; hence, no clinical data exists in children below this age. However, a paediatric treatment study is ongoing with patients aged 5 to 12 years receiving either inhaled zanamivir 10mg or placebo twice a day for 5 days.

4.5 Pregnancy and Lactation

The safety of zanamivir during pregnancy in humans has not been established. There is no information on placental transfer or secretion of zanamivir in breast milk in humans. Reproductive studies in rats and rabbits indicated that placental transfer of zanamivir occurs, and in rats zanamivir was found to be excreted into breast milk.[14]

Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri- or postnatal development of offspring following the administration of zanamivir. In a pre- and postnatal studies in the rat, zanamivir was administered to dams from day 16 of pregnancy to day 23 postpartum and no adverse effects in the development of the offspring were seen.[14]

Pregnant and lactating women were excluded from the studies in the clinical programme. However, 7 pregnancies were reported; 3 patients had received zanamivir and 4 placebo. Of the patients who had received zanamivir, 1 pregnancy spontaneously miscarried (the investigator did not consider this related to study drug), 1 pregnancy was terminated and 1 pregnancy resulted in a healthy baby born 2 weeks early. Of the patients who received placebo, 1 patient experienced uterine bleeding which resolved and the pregnancy proceeded normally; another patient who became pregnant 2 weeks after completing the study delivered a healthy infant 2 weeks early (her previous healthy pregnancy had been 3 weeks early); 1 patient experienced a spontaneous abortion at 12 weeks and 1 patient decided to terminate the pregnancy.

Animal reproduction studies are not always predictive of human response. Therefore, at this time, this drug should not be used in mothers who are breastfeeding and should only be considered in pregnancy if the possible benefit to the mother is thought to outweigh any possible risk to the infant.

5. Drug Interactions

5.1 Drug-Drug Interactions

Zanamivir is not metabolised and is predominantly renally excreted in the urine as unchanged drug, indicating a very low potential for drug interactions. Zanamivir was examined in a series of *in vitro* and *in vivo* systems to assess the potential for interactions with other coadministered therapies in the clinical setting.[18]

The renal clearance and extraction ratio of zanamivir was determined in the isolated perfused rat kidney to assess the possible effect of coadministration of several clinically relevant drugs frequently used concomitantly in influenza illness. Results indicated that clinically relevant drug interactions would not be expected to occur since cimetidine, ibuprofen, cefuroxime and pseudoephedrine elicited no significant effect on the extraction ratio of zanamivir and paracetamol (acetaminophen), and its glucuronide effected only a 16% decrease, which was likely to be the result of the elevated values of the glomerular filtration rate observed in these perfusion groups.

The possibility that zanamivir could influence the metabolism of other drug substances via an interaction with cytochrome P450 (CYP) isoenzymes was studied using probe substrates that are specifically metabolised by a single CYP isoenzyme or have a metabolite which is produced be a single isoenzyme. Zanamivir at concentrations of up to 500 μmol/L (150 mg/L) was shown to have no effect on any of the probe substrates bufuralol, chlorzoxazone, coumarin, ethoxyresorufin, mephenytoin, midazolam, phenacetin and tolbutamide (probes for isoenzymes CYP2D6, 2E1, 2A6, 1A1, 2C19, 3A, 1A2 and 2C8/9/10, respectively). This indicates that zanamivir is unlikely to affect the hepatic clearance of coadministered drugs that are cleared via CYP metabolism in humans.

In addition, there were no significant changes in the expression levels of microsomal CYP isoenzymes following daily IV administration of zanamivir (1, 9 or 90 mg/kg) for 5 weeks. These results indicate that it is unlikely that long term administration of zanamivir will affect the hepatic clearance of any substance that may be administered concomitantly.

Therefore, there is no theoretical basis for anticipating metabolic interactions between zanamivir and other coadministered compounds.

Studies in the dog and rat found the binding of zanamivir to plasma proteins to be low (<10%). Therefore, there are no implications for possible interactions with coadministered drugs that are protein bound. Similarly, a study using isolated perfused rat kidney indicated that clinically relevant drug interactions would not be expected to occur with the drugs tested (cimetidine, ibuprofen, cefuroxime, pseudoephedrine, paracetamol and its glucuronide).[18]

In vitro studies demonstrated that the potency of zanamivir against influenza virus in Madin-Darby canine kidney cells is not adversely affected in the presence of coadministered aspirin (acetylsalicylic acid) [1.2 mmol/L], paracetamol (6.6 mmol/L), ibuprofen (243 μmol/L), phenylephrine (6 mmol/L), oxymetazoline (380 μmol/L), promethazine (35 μmol/L) and amoxicillin-clavulanic acid (1.66 mmol/L). As a result, there is no indication that these commonly administered drugs for influenza-like illness would interfere with the antiviral activity of zanamivir *in vivo*.

Data from these studies are consistent with zanamivir having a low potential for interactions with coadministered drugs in the clinical setting and, hence, no formal drug-drug interaction studies have been conducted in humans (with the exception of a vaccine interaction study; see section 5.2). However, no significant drug-drug interactions were observed in population pharmacokinetic analyses of the phase I studies and the incidence of adverse events of a drug interaction nature was low in the larger phase II and III studies where a wide variety of concurrent medications, including supplied paracetamol and cough suppressants, were taken by patients.

5.2 Vaccine Interaction Study

Serum titres of antihaemagglutinin antibody, measured by haemagglutination inhibition (HAI) assay, correlate with virus-neutralising activity and are widely used as a surrogate measure of protection following influenza vaccination. Therefore, 138 patients were recruited into a placebo-controlled study to assess the effect of orally inhaled zanamivir 10mg once daily for 28 days on antihaemagglutinin antibody (HAI titre) when co-administered with Fluvirin™ trivalent influenza inactivated vaccine administered by intramuscular injection.[19]

70 patients were randomised to receive zanamivir and 68 to receive placebo. Results from this study confirmed that zanamivir does not impair the immune response to inactivated influenza vaccine in both treatment groups; similar antibody titres for all 3 vaccine antigens were achieved at 2 and 4 weeks after vaccination. Zanamivir was found to be well tolerated. The proportion of patients who experienced an adverse event was similar in the zanamivir and placebo groups (73 and 68%, respectively). The most commonly reported adverse event was headache (47% patients in the zanamivir group, 44% patients in the placebo group). The other most commonly reported adverse events were throat and tonsil discomfort and pain, nasal signs and symptoms and cough that occurred with similar incidence across the 2 treatment groups.

Blood samples were taken at screening (day 1) and post-treatment (day 29) for routine safety screening. No clinically significant differences were observed between the treatment groups for any of the laboratory parameters that were analysed.

6. Population Pharmacokinetics

The pharmacokinetics of zanamivir were evaluated using nonlinear mixed effect modelling for patients from 3 phase I and 2 phase II studies (Peng AW, et al., unpublished observations). Samples were collected from a total of 171 patients. Results demonstrated that systemic absorption of zanamivir following intranasal and oral inhalation is low and that zanamivir pharmacokinetic parameters are not significantly affected by demographic characteristics (age, gender, race, tobacco use, bodyweight and creatinine clearance), infection status or concurrent medication use.

6.1 Volunteers in Experimental Challenge Studies

A small number of serum samples were collected to evaluate and compare the pharmacokinetics of zanamivir when administered as nasal drops or spray. No meaningful differences in serum concentrations and/or pharmacokinetic parameters [absorption rate constant, area under the plasma concentration time-curve 0 to 3 hours, maximum plasma drug concentration after single-dose administration (C_{max}), time to reach C_{max}, renal clearance of the drug from plasma and fraction of the systemically available drug excreted into the urine] were observed when demographic variables and indices of infections were considered. There were no significant correlations with measures of systemic exposure and safety parameters in this study.

6.2 Patients with Naturally-Acquired Influenza

Population pharmacokinetic analyses in a small subset of patients combined with data from healthy volunteers in the challenge studies indicated that absorption of zanamivir via the intranasal route was lower than the oral inhaled route. Absorption of zanamivir was found not to be influenced by type of study (treatment or prophylaxis), demographic factors (e.g. gender, age, creatinine clearance), infection, viral titre, virus type, symptom severity (patient symptom scores) and concurrent medication use. There were no significant drug-drug interactions for patients concurrently administered drugs for symptomatic relief including paracetamol, dextromethorphan and guaiphenesin (Peng AW, et al., unpublished observations).

7. Other Influenza Antiviral Therapy

Amantadine is more widely available than rimantadine for the treatment and/or prophylaxis of influenza A virus, the latter having been used mainly in the US and Eastern Europe. Unlike zanamivir, neither shows any activity against the influenza B virus.[2] Their use may be further restricted by associated adverse effects, such as CNS complaints (nervousness, lightheadedness, difficulty concentrating), sleep problems (insomnia, fatigue) and gastrointestinal complaints, particularly at higher doses.[3] In addition, drug-resistant influenza A viruses have emerged during rimantadine treatment of uncomplicated influenza in children and adults.[20] These strains emerge rapidly during treatment, are transmissible to contacts, are genetically stable and capable of competing with wild-type viruses for transmission in the absence of selective drug pressure, and remain pathogenic.

Oseltamivir (GS4104), a neuraminidase inhibitor, is currently in phase III development for the treatment of acute influenza and prophylaxis. Published data indicate that this orally-available prodrug is associated with gastrointestinal adverse effects.[21-23] Although reported as mild and transient, the nausea and vomiting occurred consistently across all treatment and prophylaxis studies at a frequency of 2 to 3 times (nausea 6.5% in placebo group *vs* 14.7% in 75mg twice daily oseltamivir group and vomiting 3.2% placebo *vs* 11.9% oseltamivir)[24] that observed in the placebo groups.

8. Discussion

Zanamivir, a specific and potent neuraminidase inhibitor, is active against both the influenza A and B viruses. It has not been associated with emergence of resistant virus in clinical trials to date[25,26] and its impressive safety profile has demonstrated its suitability for use in a wide range of individuals in a variety of settings. Consequently, it offers significant advantages over currently available influenza antiviral therapies, fulfilling an unmet medical need. Indeed, zanamivir has already received approval in many markets for the treatment of influenza.

As zanamivir exerts its antiviral activity by the extracellular inhibition of influenza virus neuraminidase within the respiratory tract, administration via the oral inhaled route has several advantages for the management of influenza. Topical administration to the respiratory tract allows a high concentration of drug to be delivered directly to the primary site of infection without the need for high systemic exposure, thereby reducing the likelihood of adverse events or interactions with other co-administered therapies.

A comprehensive toxicology programme demonstrated that zanamivir has very low toxicity and no drug-specific toxicities despite plasma concentrations of 1336-fold greater than those for clinical use. In an attempt to identify target-organ toxicity, the maximum practical high dosage level was selected for repeat dose studies, resulting only in nonspecific effects, primarily volume-related, due to the excessive doses administered.

Clinical pharmacology studies involving the IV, intranasal and oral inhaled routes of administration in healthy patients and those experimentally infected with influenza virus found all doses of zanamivir to be well tolerated.

Data from clinical studies completed to date are extensive with over 6000 patients recruited to the phase II and III programme and 3662 having received zanamivir. In both the treatment and prophylaxis indications, the incidence of adverse events was similar between the zanamivir and placebo groups. There was little variation in the nature of adverse events reported throughout the clinical development programme, irrespective of dose, route, frequency and duration of administration.

No drug-related adverse events were observed and the most commonly reported adverse events reported by both treatment groups were nasal signs and symptoms, headache and throat/tonsil discomfort and pain, all of which are associated as symptoms of influenza-like illness. No unique or unexpected effects were observed on the haematology,

clinical chemistry or urinalysis parameters that were monitored.

The adverse event profile in the high risk population (including those patients who were old or who had underlying asthma or other chronic respiratory conditions) and paediatric patients was similar to that observed in the rest of the population. Although a limited number of elderly patients have been recruited into clinical studies to date, zanamivir was well tolerated, with adverse events occurring at a similar incidence in zanamivir- and placebo-treated patients. Since these individuals are at greatest risk from a more prolonged infection and the complications associated with influenza infection, these data are particularly encouraging.

This review of the safety profile of zanamivir, from preclinical through to clinical use, clearly demonstrates that this novel compound is well tolerated by a wide range of individuals for whom clinical use of this drug has the potential to offer significant benefit.

References

1. Nicholson KG. Clinical features of influenza. Semin Respir Infect 1992; 7 (1): 26-37
2. Monto AS. Influenza: quantifying morbidity and mortality. Am J Med 1987; 82 Suppl. 6a: 20-5
3. Van Voris LP, Betts RF, Hayden FG, et al. Successful treatment of naturally occurring influenza A/USSR/77/H1N1. JAMA 1981; 245: 1128-31
4. Dolin R, Reichman RC, Madore HP, et al. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N Engl J Med 1982; 307: 580-4
5. Woods JM, Bethell RC, Coates JAV, et al. 4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid is a highly effective inhibitor of both the sialidase (neuraminidase) and of growth of a wide range of influenza A and B viruses in vitro. Antimicrob Agents Chemother 1993; 37: 1473-9
6. Ryan DM, Ticehurst J, Dempsey MH, et al. Inhibition of influenza virus replication in mice by zanamivir (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid) is consistent with extracellular activity of viral neuraminidase (sialidase). Antimicrob Agents Chemother 1994; 38: 2270-5
7. Hayden FG, Treanor JJ, Betts RF, et al. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. JAMA 1996; 275: 295-9
8. Hayden FG, Lobo M, Hussey EK, et al. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In: Brown LE, Hampson AW, Webster RG, editors. Options for the control of influenza III. Amsterdam: Elsevier Science B.V, 1996: 718-25. (Int Cngr Ser; 1123)
9. The MIST Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998; 352: 1877-81
10. Fleming D, Makela M, Pauksens K, et al. High-risk and otherwise healthy patients demonstrate alleviation of influenza symptoms 2-5 days earlier following inhaled zanamivir treatment: European study - winter 1997/8 [abstract 789]. 36th Annual Meeting of the Infectious Diseases Society of America: 1998 Nov 12-15: Denver, CO
11. Monto AS, Robinson DP, Herlocher ML, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in prevention of influenza among healthy adults. JAMA 1999; 282 (1): 31-5
12. Matsumoto K, Ogawa N, Nerome K, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. Antiviral Ther 1999; 4: 61-8
13. von Itzstein M, Wu W-Y, Kok GB, et al. Rational design of potent sialidase-based inhibitors of influenza virus replication. Nature 1993; 363: 418-23
14. Dines GD, Bethell R, Daniel M. Preclinical development of low toxicity drugs; focus on zanamivir, an anti-influenza drug. Drug Saf 1998; 19 (3): 233-41
15. Cass LMR, Bye A. Repeat inhaled doses of zanamivir dry powder do not affect pulmonary function and bronchial hyper-responsiveness in asthmatic subjects. Respir Med. In press
16. Cass LMR, Efthymiopoulos C, Marsh J, et al. Effect of renal impairment on the pharmacokinetics of zanamivir. Clin Pharmacokinet 1999; 36 Suppl. 1: 1-11
17. Schilling M, Povinelli L, Krause P, et al. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. Vaccine 1998; 16 (18): 1771-4
18. Daniel MJ, Barnett JM, Pearson BA. The low potential for drug interactions with zanamivir: a review. Clin Pharmacokinet 1999; 36 Suppl. 1: 41-50
19. Webster A, Boyce M, Edmundson S, et al. Co-administration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of anti-haemagglutinin antibodies (HAI) titre in healthy volunteers. Clin Pharmacokinet 1999; 36 Suppl. 1: 51-8
20. Hayden FG. Amantadine and rimantadine resistance in influenza A viruses. Curr Opin Infect Dis 1994; 7: 674-7
21. Treanor JJ, Vrooman PS, Hayden FG, et al. Efficacy of oral GS4104 in treating acute influenza. Final Program, Abstracts and Exhibits Addendum of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-28; San Diego (CA), 21
22. Aoki F, Osterhaus A, Rimmelzwann G, et al. Oral GS4104 successfully reduces duration and severity of naturally-acquired influenza. Final Program, Abstracts and Exhibits Addendum of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-28; San Diego (CA), 22

23. Hayden FG, Atmar R, Schilling M, et al. Safety and efficacy of oral GS4104 in long-term prophylaxis of natural influenza. Final Program, Abstracts and Exhibits Addendum of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-28; San Diego (CA), 22
24. Nicholson KG, Ward P, Kinnersley N. Oseltamivir is an effective treatment for influenza and reduces influenza related complications and need for antibiotics [abstract]. J Antimicrob Chemother 1999; 44 Suppl. A: 41-2
25. Barnett J, Dempsey M, Tisdale M, et al. Susceptibility monitoring of influenza virus clinical isolates to the neuraminidase inhibitor zanamivir (GG167) during phase II clinical efficacy trials. Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28-Oct 1; Toronto, Canada, 230
26. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. J Infect Dis 1999: 180: 254-61

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