EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Invirase

(Saquinavir Mesilate)

Procedure No. EMEA/H/C/000113/P46/0054

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I.INTRODUCTION

Roche submits, in accordance with Article 46 of Regulation (EC) N°1901/2006, to the EMA the final report for study
"NV20911 – A phase I/II study of Invirase boosted with ritonavir in HIV infected infants and children 4 months to less than 6 years old"

Previous studies PACTG397 and HIVNAT017 have provided data on the pharmacokinetics, safety and activity of saquinavir boosted with low dose ritonavir in HIV-infected children aged 4 to 16 years old. However, these studies were restricted to those subjects who were able to swallow capsules or tablets.

Study NV20911 was therefore designed to investigate the pharmacokinetics, safety and antiviral activity of saquinavir/ritonavir in combination with background ARVs in HIV-1 infected infants and children 4 months to <6 years of age. For children who could not swallow capsules, the capsules were opened and the powder mixed with a vehicle before the dose was administered following a meal.

II.PRODUCT DEVELOPMENT RATIONALE

The purpose of this file is to summarize paediatric data on ritonavir-boosted Invirase collected by the MAH in a study with infants and children that has not been previously submitted to EMA.

III.SUBMITTED DATA

Study NV20911

An open label, multicenter study in HIV infected infants and young children stratified into 2 groups.
• Group A: Infants 4 months to <2 years old
• Group B: Children 2 years to <6 years old

Objective(s):

Primary

1. To evaluate the pharmacokinetics of saquinavir that, when boosted with ritonavir, provides a systemic exposure in HIV-1 infected infants and children 4 months to <6 years similar to that which has been shown to be safe and effective in older children and adults.

2. To determine the safety and tolerability of saquinavir when boosted with ritonavir in HIV-1 infected infants and children 4 months to <6 years of age.

Secondary

1. To characterize the pharmacokinetics of ritonavir when given as a booster in combination with saquinavir in HIV-1 infected infants and children 4 months to <6 years.
2. To evaluate the antiviral activity of saquinavir when boosted with ritonavir against HIV-1 infection in infants and children 4 months to <6 years.

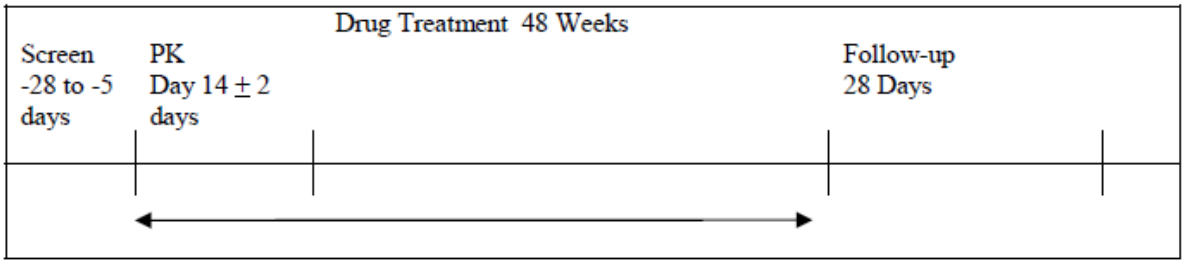
Number of subjects:

18 (5 patients 4 months to <2 years old and 13 patients 2 years to <6 years old)

Diagnosis and Criteria for Inclusion:

HIV-1 infected infants and children 4 months to <6 years of age who, in the judgment of the investigator, had a medical need for boosted PI therapy were to be included in the study.

Duration of Treatment:



Dosage and Administration:

Patients received

- saquinavir mesylate (Invirase 200 mg HC and/or Invirase 500 mg FCT) 50 mg/kg BID up to the adult dose of 1000 mg BID and
- ritonavir (Norvir 80 mg/mL oral solution) 3 mg/kg BID for children weighing 5 to 15 kg or 2.5 mg/kg BID for children weighing 15 to 40 kg up to a dose of 100 mg for children weighing >40 kg BID
- in combination with other ARVs.

At home saquinavir and ritonavir were to be taken concomitantly with food. On days on which blood sampling for pharmacokinetics occurred, dosing in the morning was to occur approximately 30 minutes after the start of breakfast.

Patients could revise their ARV regimen when initiating saquinavir and ritonavir:
Patients with a viral load <50 copies/mL at study entry could continue on pre-study nucleoside; patients with a detectable viral load had their nucleoside background ARV regimen optimized based on prior history, and results of genotypic resistance testing at screening, if possible. All patients had to be receiving >2 nucleoside ARVs as background therapy in combination with saquinavir/ritonavir (lopinavir was also allowed).

For patients who could not swallow saquinavir capsules, the 200 mg capsule(s) were opened and the contents of the capsule administered in a vehicle [sugar syrup (sorbitol syrup for children with diabetes mellitus or glucose intolerance), jam or baby formula] and ritonavir oral solution. The choice of vehicle was determined by patient/caregiver preference. Vehicle could be changed during the course of the study. If the child started the study using opened saquinavir capsule(s) and then was able to swallow capsules/tablets, the child could switch to closed capsules/tablets. Instructions to prepare the medication were provided in the protocol.

For patients who could swallow capsules and or tablets no vehicle was required. The Invirase 500 mg FCT was not to be crushed prior to administration.
Norvir was dosed with a calibrated dosing syringe.

Assessor's comments:
Only one European centre included 8 Caucasian patients, the other patients were of Oriental origin. Mean age was 0.8 years in group A and 4.0 years in group B; mean weight was 9.4kg and 15.2kg in group A and B, respectively.
Looking at the data listings only three children of the High Age Group were able to swallow Invirase capsules. All others received medication by opening the capsules and mixing the contents with different vehicles, which might have introduced considerable variability.

Previous Medications

Previous Antiretroviral Therapy
Ninety four percent (17/18) of all patients reported at least one previous antiretroviral therapy at screening. One patient in the High Age Group had no previous antiretroviral experience.
Nucleoside analogues were the most commonly reported previous antiretroviral treatment with lamivudine (67%; 12/18) and zidovudine (39%; 7/18) being the most frequently used previous treatment in this class among both age groups.

Concomitant Medications

Concomitant Antiretroviral Treatment

All 18 patients were receiving concomitant antiretroviral treatment at baseline. Nucleoside/nucleotide analogues were the most commonly used concomitant antiretroviral treatment at baseline with lamivudine (100%, 18/18 patients), zidovudine (67%, 12/18 patients) and didanosine (28%, 5/18 patients) being the most commonly used agents in this class.

Assessments:

Assessment/Procedure	Screen (days)	Treatment (weeks)											Follow Up
	-28 TO -5	Baseline	PK(hours)[a] Day 14 ± 2					4	8	12	24	36	48[b]	4 week[c]
			Pre-dose	3	4	8	12							
Informed Consent	x													
Medical History (including CDC classification of HIV infection)	x													
Physical Examination	x	x									x		x	
Body Height and Weight	x	x	x					x	x	x	x	x	x	x
Vital Signs	x	x	x	x			x	x	x	x	x	x	x	x
GT resistance testing to ARVs[d,e] (2.0 mL)	x												x	
ECG[f]	x													
Urinalysis (dipstick)[f]	x								x		x		x	
PK samples for SQV and RTV[g] (5.4mL)			x	x	x	x	x		x[h]	x[h]	x[i]			

a) PK assessments after Day 14 (± 2 days), or Day 28(± 2 days) for patients switching from an NNRTI containing regimen at baseline. If a dose adjustment was required a repeat PK sampling was to be performed at a mimimum of 14 days after the dose adjustment.
b) Or upon premature discontinuation
c) Follow-up visit 4 weeks after discontinuation of therapy, for any reason.
d) If there was not already a value available taken within the previous 4 weeks.
e) GT resistance testing at screening, at confirmed virological failure, or study drug discontinuation, or week 48, or premature discontinuation.
f) If clinically indicated at the discretion of the Investigator.
g) A heparin lock or similar device could be used to minimize discomfort to patients. When using such a device, it was to be back-flushed with heparinized saline following each blood draw, and the first 0.2 mL of blood volume from consecutive draw discarded. When utilizing a heparin lock or similar device, the volume of blood was 0.7 mL. The maximum amount of blood drawn for PK assessments was 5.4 mL.
h) Sample collected pre-dose.
i) Sample collected pre-dose and at 4 hours post dose.

Results

Treatment Adherence

Patients and their parent/caregiver were counselled on the importance of adherence to antiretroviral drugs at each study visit where assessments of adherence were performed by retrospective questioning and investigator assessment.

The trial treatment was in general well accepted with a high degree of adherence. The saquinavir dose was missed on one ore more occasions by three patients.

Disposition of patients

Two patients were withdrawn prematurely from study treatment during the study period. One of these patients (118176/4101) completed all scheduled study assessments.
Patient 118168/1302 a Caucasian male patient <1 year of age was withdrawn from study treatment on day 73. The reason for withdrawal was given on the CRF as 'failure to return'.
Patient 118176/4101, a one year-old Oriental female patient was withdrawn from SQV/r treatment on day 84 (due to insufficient SQV/r levels). The reason for withdrawal was given on the CRF as 'insufficient therapeutic response'.

Assessor's comments:
Two patients were withdrawn prematurely from study treatment during the study period.

Pharmacokinetics

Saquinavir

	< 2 years:	**2-6 years:**
Dose range (mg):	400 – 600	600 – 1000
AUC_{0-12h} range (hr*µg/ml):	2.10 – 43.8	4.77 – 83.2
C_{max} range (ng/mL):	331 - 6860	954 – 12100
C_{trough} range (ng/mL)	26.6 – 1090	470 – 6420
$T_{1/2}$ (hrs)	2.27 – 2.66	2.15 – 5.25
Adjusted to 50mg/kg (%CV,range):		
AUC_{0-12h} (hr*µg/ml):	18.7 hr (107%, 1.59 to 49.3)	38.0 (48%, 13.5 to 61.5)
C_{max} (ng/mL):	2910 (107%, 251 to 7720)	5570 (50%, 2000 to 9160)
C_{trough} (ng/mL)	645 (83%, 23.6 to 1120)	1860 (57%, 563 to 3980)
Dose adjustment:	2/5	3/13
Targeted c_{trough}:	4/5	10/13

Ritonavir

In general, dose normalized ritonavir exposures appeared to be higher the High Age Group patients: 13.6 vs. 21.8 hr*ug/mL for AUC_{0-12h}, 577 vs. 995 ng/mL for C_{trough}, and 2050 vs. 3370 ng/mL for C_{max} (table not shown). In addition, dose normalized ritonavir exposures were in general comparable to the exposures observed in the HIVNAT 017 study.

Assessor's comments:

*In the low age group (A), saquinavir doses ranged from 400 mg to 600 mg. As expected, the exposure parameters exhibited a large inter-patient variability: AUC0-12h ranged from 2.10 to 43.8 hr*ug/mL, C_{max} ranged from 331 to 6860 ng/mL, and average C_{trough} ranged from 26.6 to 1090 ng/mL.*

*In the high age group (B), saquinavir doses ranged from 600 mg to 1000 mg. Similar to Group A, the exposure parameters exhibited a large inter-patient variability: AUC0-12h ranged from 4.77 to 83.2 hr*ug/mL, C_{max} ranged from 954 to 12100 ng/mL, and C_{trough} ranged from 470 to 6420 ng/mL. However, the t1/2 was comparable across patients ranging from 2.15 to 5.25.*

The prescribed dose of 50 mg/kg of saquinavir boosted with the prescribed dose of ritonavir BID was adequate to achieve the desired C_{trough} values in 10 of 13 patients.

Efficacy

HIV-1 viral load

	< 2 years:	2-6 years:
Baseline assessment:	5	13
12 wks assessment:	4	13
24/48 wks assessment:	3	13
Mean viral load (baseline)*:	3.50	3.53
Mean change from baseline (48 wks)*:	-1.27	-1.39
< 400 copies/mL (48 wks):	2/3 (2/5)	11/13
< 50 copies/ml (48 wks):	2/3 (2/5)	9/13
> 1 log decrease (48 wks):	1/3 (2/5)	7/13
Virological failure:	3/5	1/13

* $\log_{10}$ copies/mL

CD4/CD8-cell count

	< 2 years:	2-6 years:
Baseline assessment:	5	12
12 wks assessment:	4	13
24/48 wks assessment:	3	13
Mean (median) CD4 cell count*:	1719 (1212)	1183 (935)
Mean (median) CD4 change (48 wks)*:	-50 (-562)	+126 (-15)
Relative CD4 change (48 wks):	+2.21%	+2.97%
Mean (median) CD8 cell count*:	2261 (2537)	1572 (1493)
Mean (median) CD8 change (48 wks)*:	-92 (-300)	+40 (-17)
Relative CD8 change (48 wks):	-2.3%	-1.5%

* cell/µL

Mean change in body height and body weight z-scores at 48 weeks were -0.05/+0.07 for the Low Age Group and +0.55/+0.01 in the High Age Group.

No CDC category B and C HIV related illnesses were reported during the trial.

Assessor's comment:
The chosen parameters for antiretroviral activity are acceptable and show that in general children responded to treatment over the duration of the study. Results are comparable to an earlier study in HIV-1 infected children aged 4 to 15 years receiving dual lopinavir/saquinavir based HAART (Roche Clinical Study Report – Protocol ML19540). While results between treatment groups appear to be similar, the Low Age Group is too small to allow a definite conclusion. In the high age group, 11 of 13 children had <400 HIV-1 copies at week 48 and the relative CD4 cell count change at week 48 was approx. 3%; there was 1 virological failure in that group.

Safety
Overall, 78% (14/18) of patients reported at least one adverse event during the study. All 5 patients in the Low Age Group (100%) and 9/13 patients (69%) in the High Age Group reported adverse events.

'Infections and Infestations' was the class of adverse event most frequently recorded, being reported in 56% (10/18) of patients. Three of the 5 patients in the Low Age Group and 7/18 (54%) of patients in the High Age Group recorded at least one adverse event in this body system class. Bronchitis, recorded in 3 patients in the High Age Group was the only individual adverse event in this body system reported in more than one patient.

Gastrointestinal disorders were the next most frequently recorded adverse events being reported by 44% (8/18) of patients. Dental caries reported in 1 patient in the Low Age Group and 2 patients in the High Age Group, diarrhea reported in in 3 patients in the High Age Group, vomiting reported in 1 patient in the Low Age Group and 2 patients in the High Age Group and constipation reported in 2 patients in the Low Age Group were the only events reported in more than 1 patient each.

Four of the eighteen patients (22%) experienced at least one adverse event during the study which was considered related to trial treatment by the investigator.
Vomiting which was considered related to trial treatment by the investigator was experienced by 1 patient in the Low Age Group and 2 patients in the High Age Group. Other related adverse events reported in single patients in the High Age Group were abdominal pain lower and diarrhea.

No deaths were reported during the 48 week study.
Three patients experienced a serious adverse event during the course of the study.
One patient in the Low Age Group and 1 patient in the High Age Group experienced pneumonia; 1 patient in the High Age Group experienced bronchitis.

Nine patients experienced an elevation in blood triglyceride levels during the study and 5 patients experienced an elevation in LDL-cholesterol. The elevations observed were mostly less than Grade 2 (ACTG laboratory grading), requiring no treatment intervention and were no worse than in other studies of PI based HAART in children.

Assessor's comment:
Three patients experienced a serious adverse event during the treatment period, which were considered unrelated to trial treatment and resolved without sequelae.
All other reported adverse events were mild or moderate in intensity and the most commonly reported individual events were bronchitis, dental, caries, diarrhoea and vomiting. Four patients experienced five adverse events considered related to trial treatment. These events were vomiting (3 patients), abdominal pain lower (1 patient) and diarrhea (1 patient).
There were no deaths during the 48 weeks study period and no HIV-related illnesses were reported. No new or unexpected adverse reactions were seen.
In summary, the safety of saquinavir/RTV in children of <6 years at the given dose appears to be similar to that in adults.

IV.CONCLUSION AND RECOMMENDATION

MAH conclusion
The NV20911 study was specifically designed to evaluate pharmacokinetics of ritonavir boosted saquinavir at exposures similar to that which had been shown to be safe and effective in older children and adults, and to determine the safety and tolerability in children. The study was designed as a non-comparative open label study.
The NV20911 study met the stated study objectives, and demonstrated pharmacokinetics, safety and tolerability of ritonavir boosted Invirase in paediatric patients 2 years to <6 years of age at systemic exposures of saquinavir that had previously been demonstrated to be safe and effective in older children and adults.

In addition, the study demonstrated substantial and sustained viral suppression and stability in CD4 lymphocyte counts, further validating the extrapolation of efficacy from adult studies to the pediatric population. Thus, the benefit /risk assessment for use of ritonavir boosted Invirase as part of an ARV regimen in children 2 to <6 years of age is positive.

Assessor´s conclusion:
In this multicentre, open-label trial 18 HIV-1 infected children of less than 6 years of age were treated with ritonavir-boosted Invirase in combination with other HIV-medications for 48 weeks. Invirase was given at a dose of 50 mg/kg BID up to the adult dose of 1000 mg BID. All but one child were pre-treated with different ARV regimens reflecting predominant use of Invirase as a second line treatment in clinical practice. All children received concomitant ARV treatment as required in the Invirase SPC.
For patients who could not swallow the capsules, the 200 mg capsule(s) were opened and the contents of the capsule administered in a vehicle. It is noted that with the applied dosing approach less precise dosing is possible which led to a highly variable exposure. Therefore a paediatric formulation (e.g as a liquid) would in principle be the preferred option.

Data on children below 2 years (3 of 5 children evaluable at week 48) is too limited to give any recommendation.

In the small sample of children between 2 and 6 years of age the dosing regimen resulted in adequate pharmacokinetic exposure. Target C_{trough} levels were reached in 10 of 13 patients, otherwise dose adjustments were made based on day 14 PK assessment. Eleven of 13 children had <400 HIV-1 copies at week 48 and the relative CD4 cell count change at week 48 was approx. 3%; there was 1 virological failure in that group. The nature of the safety profile was similar to that reported in adults.
In summary the dosing range of 600-1000mg in this study was safe and effective in this age group.

Findings in this small sample of children between 2 and 6 years of age are not sufficiently robust to consider granting a paediatric indication for Invirase. However inclusion of the generated information in the SmPC could be useful to inform physicians on PK, efficacy and safety with the proposed dosing regimen.

Comments:
We surely cannot concur with the Applicant's conclusion that "the benefit /risk assessment for use of ritonavir boosted Invirase as part of an ARV regimen in children 2 to <6 years of age is **positive**" when considering that
- only 13 paediatric patients from 2 to 6 years old were included in this phase I/II study;
- a large inter-patients variability in saquinavir dose and exposure was observed;
and given the recent safety signal on QT prolongation raised through a dedicated study.

We endorse the Rapporteur's conclusion that data issued from NV20911 study are not sufficiently robust to consider granting a paediatric indication of Invirase, and we even question the relevance of reflecting these unreliable data in the SPC.
As a matter of fact, if any statement is to be made as regards this paediatric use it should consists of describing the high PK variability and the limited clinical data **precluding any proper benefit/risk assessment.**

Assessor's comment:
We agree with the positions that the data are too limited to allow a proper benefit risk assessment. However, reporting the results of the study with regard to PK and safety data in the higher age group is considered meaningful. Limitations of these data should be made clear when describing the study in section 5.1.

V.REQUEST FOR SUPPLEMENTORY INFORMATION

The MAH should submit a proposal for an update of relevant sections of the SmPC with the data generated in the age group between 2 and 6 years.

It could be considered to include PK data in section 5.2 and the safety profile in section 4.8. Consideration should be given to describe the trial results in section 5.1 of the SmPC.