GW 433908, fosamprenavir, Lexiva®

NDA 21-XXX

And speaking of boosting…

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Position statement

Based on data from ongoing and completed studies, and to the extent the sponsors have provided requested information, TAG and the undersigned organizations and patient advocates of the community of people living with HIV/AIDS support the full approval of the GSK/Vertex application to FDA of Lexiva® brand 908 (fosamprenavir, NDA 21-XXX) to treat HIV infection in combination with other antiretroviral agents in adults. However, we support the approval of 908 only in combination with low-dose ritonavir (908/r) (see Executive Summary and Section 3).

We underline the sad state of affairs regarding the FDA's inability to enforce important post-marketing studies that need to be carried out, and with a sigh truly hope that the follow-up (Phase IV, post-marketing) studies are completed in as short a time as possible (see Section 7).

Executive Summary

FDA granted accelerated approval to Agenerase® brand amprenavir (NDA 21-007 and NDA 21-039) in April 1999. 908 allows us an opportunity to get an easier-to-use drug from the same molecule.

In fact, over the last four years, clinical management questions have not been studied by the sponsors, and the drug has languished around the 5% mark of protease inhibitors used. This may have to do with uncertainties about how to best use amprenavir as much as with the high pill burden (16) per day. The only two important interaction studies completed since 1999 (which both took more than two years to complete) are for methadone and oral contraceptives.

How should 908 be used? Two of the three open label studies done - Solo and Context – have clearly demonstrated that 908, like amprenavir itself, is more potent when boosted with ritonavir. We see no reason to approve another mediocre PI (without /r). (See sections 4 &6).

In the July 2003 DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, amprenavir is recommended only with ritonavir as an alternative PI-based regimen (table 12a). (see Section 3).

Is 908 effective? In all studies to date, this drug has been seen as a mediocre PI. In the language of the trial design, it has been seen as non-inferior to (as potent as?) NFV, although not non-inferior (inferior?) to lopinavir/ritonavir (Kaletra®, LPV/r). The sponsor's development strategy utilized non-inferiority designs, with an AAUCMB statistical analysis (see Section 3).

Does the AAUCMB analysis "forgive" a large dropout rate? All studies had significant rates of drop-outs (~30% in the better arms).

908 has been analyzed in an advanced yet naïve or less advanced but experienced population, but not in a non-advanced population, nor has there been head-to-head comparison with amprenavir or an expanded access program (EAP) of any type.

Co-administered with ritonavir, it is more potent both clinically and virologically. (In Solo, of the few who failed virologically in the 908/r arms, it was due to NRTI resistance and not PI resistance.)

What are the benefits of 908? Unlike amprenavir, 908 does not have major GI tract side effects, reducing from approximately 70% to 5-9% (grades 2-4). 908 also gets better marks than its predecessor regarding rash, with incidence at 2-7% as compared to ~27% with amprenavir. Lab abnormalities do not reach 2% at 24 weeks.

The pill burden for 908 (one pill BID) is greatly reduced from amprenavir (eight pills BID), because it is more water-soluble and is now in line with the pill count of the majority of PIs. We mustn't forget the one extra pill (ritonavir) with each administration.

What are the risks of 908? The lack of an expanded access program for 908 may leave the community at a disadvantage in assessing the product in real life. The lack of data comparing 908 to Agenerase® raises many questions regarding bioequivalence, not least in the panoply of drug/drug interactions (see Interactions section and Appendix 1).

The community is greatly concerned that as a sulfa drug, the use of 908 needs to be monitored when administered with other sulfa drugs (see Section 4) .

The overall incidence of drug-related adverse events, grades 2-4, is statistically similar between 908/ABC/3TC and NFV/ABC/3TC (30% vs 34% respectively) (Neat) and between 908/r/ABC/3TC and NFV/ABC/3TC (41% vs 39%) (Solo). (see Section 5).

What is unknown about 908?

- Influence of sex/gender on efficacy, side effects and toxicities
- Influence of race/ethnicity on efficacy, side effects and toxicities
- Pediatric dosing
- Liquid formulation
- The clinical relevance of the I50V/L mutation
- QD dosing vs BID
-

We cannot say if 908 is effective in specific populations because the stratified data has not been made available. 908 has not been looked at head-to-head with amprenavir, nor has there been an expanded access program (EAP).

FDA oversight of Phase IV, as previously implied, is a lion without teeth. Companies agree to do trials with FDA, and are reminded ad infinitum that they need to be done; if they are not, FDA can pull a drug from the market. This has never happened in the history of the HIV pandemic. 908 is the 19th anti-HIV drug to be approved. Is it time to start pulling approved HIV drugs off market when Phase IV commitments have not been honored? (see Section 7).

Who will benefit from 908? There are many ill-defined aspects of this drug, including interactions, side effects and resistance, all of which would have been helped through an EAP. The generous EAPs of amprenavir, which tried to look at questions on lipodystrophy and double PIs, were abandoned in the 908 development program (see Appendix 2).

We urge GSK and Vertex to price 908 cost neutral with Kaletra® to afford the greatest number of people the option of using the drug.

If you want to know more…

1. Background

Fosamprenavir (908, Vertex Pharmaceuticals, licensed to GlaxoSmithKline) is the calcium phosphate ester pro-drug of the protease inhibitor amprenavir (Agenerase®, GSK). Vertex and GSK will share the rights to 908 in the United States, Europe and parts of Asia.

The cosponsors submitted a New Drug Application to FDA in December 2002. The FDA did not give it a priority review. A decision is expected by 19 October 2003.

Amprenavir received its marketing license four years ago; see TAG's February 1999 position paper at http://www.aidsinfonyc.org/tag/activism/ange.html. It is both FDA and EMEA approved.

Administering 908 with low dose ritonavir results in greater antiviral activity. In April 2001, FDA recommended that amprenavir be boosted with 100mg Norvir® (ritonavir) BID. Further, the only mention of Agenerase® is with/r in the most recent DHHS guidelines.

2. Pre-clinical data & Dosing

The suggested minimum target trough concentrations are 400 ng/mL for Agenerase®. The serum half-life is 7.1 – 10.6 hours. There is no intracellular half-life data.

Prodrug 908 (a toxicologically inert chemical) is rapidly hydrolized to APV, the biologically active product, during absorption with negligible 908 systemic exposure. In HIV+ patients, plasma APV concentrations decline by approximately 30% over 2-4 weeks until steady state is achieved.

Plasma levels are "time-variant" and "inconsistent". Given this "multifactorial" data, the addition of ritonavir (/r) makes it a more stable drug (achieving an improved steady-state concentration of amprenavir).

Amprenavir does not penetrate in any significant way into the brain or testes.

700 mg BID of 908 appears to have potent antiviral activity in humans. In a poster at the 8th CROI, GSK showed that 1400mg of 908 was equal to 1200mg of Agenerase® in area under the curve, but not in either Cmax (30% lower) or Cmin (28% higher). For this reason (differences in bioequivalence probably due to absorption issues), the Phase III program was set up to show 908's safety, efficacy and tolerability.

Due to stability, IQ (potency), and resistance, and because it is the only indication the sponsors are asking for in Europe, we believe the dosing must be approved 908/r (see Sections 3 and 5).

The inhibitory quotient

To assess the in vitro potency relative to achievable PI concentrations, IQ is a way of comparing potencies. In a paper at the 43rd ICAAC, protein-binding adjusted IC50 values for PIs were determined in at least two sets of measurements. Steady-state Cmin from published reports was used to calculate IQ.

Potency of PIs	
Published mean (95% CI) Cmin mcg/mL	Estimated mean (95% CI) for IQ based on measured invitro IC50
amprenavir (APV) 0.496±0.121;	
APV/r 1200/200mg QD, 1.36 (1.12-1.67)	2.7, na
APV/r 600/100mg BID, 1.32 (1.02-1.86)	2.7, na
fos-APV 1395mg BID, 0.325 (na)	0.7, na
fos-APV/r 1395/200mg QD, 1.45 (1.16-1.81)	2.9, na
fos-APV/r 700/100mg BID, 2.12 (1.77-2.54)	4.3, na

Potency of PIs	
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Several approaches are being used to calculate IQs. In study ANRS-104, the inhibitory concentration and the virtual inhibitory quotient were the best predictors of APV/r virological response.

One interesting poster at ICAAC suggested that IQ cannot be used at a population level, which does not preclude its use individually (patient by patient). In that poster, they did calculate the APV IQ to be 0.6 for 1200mg BID, 2.1 for 1200/200mg QD (/r) and 3.3 for 600/100mg BID (/r).

Protein-binding correction and concentration-dependent binding

IQ should not be used for drug comparison, until assay standardization for protein binding has been achieved.

	APV BID	IDV Q8h	RTV Q12
IC50 (WT) (ng/ml)	14.6	21.3	46.6
Protein-binding			
Induced fold shift	5.0	2.3	17.8
Corrected IC50 (ng/ml)	75	49	829
Average Cmin (ng/ml)	326	152	3067
Cmin/IC50	4.3	3.1	3.7

Estimated IC50 shifts for some PIs (HIV-1 IIIB strain compared with population steady-state trough levels from the literature)

In conclusion, the IQ for Agenerase, and probably 908, is much higher with /r (see Appendix 4).

3. Efficacy studies

Here we review the three pivotal efficacy studies of 908 – Neat, Solo and Context

Neat study

Neat was an open-label study in ART naïve subjects comparing the efficacy and safety of 908 to NFV over 48 weeks. Two hundred and fifty one (249 treated) subjects with plasma HIV-1 RNA (vRNA) = 5000 copies/mL were randomized 2:1 to 908 (1400mg BID) or NFV (1250mg BID) plus the same NRTI background of abacavir + lamivudine. All subjects were stratified at entry based on RNA. Neat looked at safety and was analyzed using AAUCMB.

The study was conducted in the USA, Panama, Puerto Rico, and South Africa. 31% of participants were women. The population (24% white, 32% black, and 44% Hispanic) had similar baseline attributes: median HIV-1 RNA (range) was 4.82 (1.7–7.4) and 4.85 (2.5–6.6) and CD4 were 211 (2–1136) and 213 (2–985) for 908 and NFV, respectively. Approximately 45% of subjects had RNA >100,000 c/mL and 48% had CD4 cells < 200 cells/mm^3. 18% of subjects had CD4 < 50 cells/mm^3.

Thirty percent (908) and 46% (NFV) of subjects prematurely discontinued the study (see discontinuation chart below, which does not include clinical progression at 1% and death at 2%). The median CD4 change from baseline was +201 and +216 cells/mm^3 on 908 and NFV, respectively.

Neat results

48 week virologic data (ITT RD = F)	908 BID n = 166	NFV BID n = 83	Stratified D (95% CI)
vRNA % < 400 c/mL	66%	51%	15% (2%, 28%)
vRNA % < 50 c/mL	55%	41%	14% (2%, 27%)
AAUCMB (log 10 copies/ml)	-2.41	-2.32	-0.082 (-0.333, 0.169)

Failures due to adverse events and other non-virologic reasons were comparable between the NFV and the 908 groups (~21%). The difference was in virologic failures: 14% in the 908 group vs 28% in the NFV group. Four percent of people prematurely discontinued the study due to insufficient viral load response in the 908 group vs 13% in the NFV group. CD4 increases were about the same in each group: 201 vs 216.

There was more hypersensitivity due to abacavir (ABC) in the 908 group (9% vs 5%) and more rash in the 908 group (7% vs 2%). Why were there more ABC hypersensitivity reactions in the 908 arm? The remaining clinical adverse events profile between the 2 drugs were comparable: nausea 4-5%, vomiting 2-4%, fatigue 1-2%, headache 2%, insomnia 1-2%, weakness 1-2%. Liver elevations and cholesterol counts were similar in both arms.

Solo study

The Solo study was powered on proportions of patients under 400 and 50. Using this more traditional analysis, 908/r once daily vs NFV BID (all with ABC/3TC) were compared. 660 treatment-naïve patients were randomized. About 27% of study participants were female; 51% white, 38% black, 7% hispanic. 7% had hepatitis B, 18% had hepatitis C. 21% had experienced a CDC class C event. The average HIV viral load was about 63,000 copies/ml and CD4 count was 170. 20% of people had < 200 CD4 count.

Solo results

Outcomes (ITT RD=F)	908/r QD	NFV BID
Viral failure (overall)	7%	17%
Viral rebound	6%	9%
Never achieved Viral load suppression	<1%	2%
Prematurely discontinued	<1%	7%
	Premature discontinuations	
Adverse events	8%	5%
Lost to follow-up	6%	3%
Consent withdrawn	5%	3%
Other	5%	3%
	Percent of Patients with HIV RNA <400 c/ml	
At Week 48 (ITT M=F)	68%	65%
Percent with HIV RNA <50 copies/ml (ITT M=F)	56%	52%
CD4 Increase	+396	+385

Context Study

The Context Study was a 24-week (with extension to 48 weeks) efficacy and safety look at 908/r vs lopinavir/r in PI-experienced people. People had prior experience with at least 1 or 2 protease inhibitors. People could be NNRTI naïve or experienced. There was no CD4 criteria. This was a non-inferiority analysis in which 908 had to show non-inferiority to LPV/r. The study took place in Europe, US, Chile, Puerto Rico, Canada, and Australia. The people in this study were fairly advanced in terms of HIV progression; 33% had a history of CDC class C events. BL CD4 counts ranged between 234 and 290. Tenofovir was available for people in this study and was part of about > 50% of regimens in all three arms. Context was powered on AAUCMB.

The eligibility criteria required resistance testing and permitted entry into the study only if at least two nucleoside reverse transcriptase inhibitors retained sufficient activity. The interpretation of the genotype was done via guideline rules from Visible Genetics. These rules were updated during the course of the study as new information became available.

LPV/r performed better than 908/r virologically. Viral load reduction, as evaluated by the mean time-averaged change from baseline at 24 weeks, was -1.48 log in the 908 QD group, -1.50 log in the 908 BID group, and -1.66 in the LPV/r group.

Virologic Results (ITT R/D=F) (24 weeks)

% <400 copies		% <50 copies	
58%	908/r qd	40%	908/r qd
60%	908/r bid	42%	908/r bid
69%	LPV/r	48%	LPV/r

AAUCMB

Oddly, viral load decreases were not calculated. The actual viral load was not a primary endpoint, although the percentages below 400 and 50 were a secondary one. Thus, viral load change was recorded, simply not reported. That information may help us see by how inferior 908/r is to LPV/r. In other words, the final drop could have been a whole log lower for some people, and could have differentiated the two treatments even more. Was AAUCMB used in order to compare 908 to LPV/r without 908 losing? AAUCMB is a technique recognized by the FDA in studies where a majority of people are not expected to achieve complete viral suppression (BLD). In at least two of the three arms, there was no reason not to expect viral load to reach the limit of detection, as baseline viral load averaged 14,000 copies. LPV/r can do that with one eye shut. 908/r BID has been previously shown to achieve such results). AAUCMB probably underestimates the efficacy of therapy in people who achieve suppression, especially if they start with relatively low viral loads at treatment initiation. The AAUCMB's endpoints are less sensitive to missing data.

908/r was compared against the recommended PI standard of care (LOP/r + 2 nukes). Even though it lost, death and progression can be avoided. Analyzing viral load decreases, what would the data look like?

Context study results (II)

	908/r QD	908/r BID	LPV BID
Virologic failure	34%	27%	21%
RNA rebound	9%	7%	11%
Never achieved VL suppression	22%	17%	11%
Non-virologic failures	8%	10%	9%
Adverse events	<1%	<1%	6%
Lost to follow-up	4%	7%	2%
Consent withdrawn	2%	0%	<1%

In Context, 543 people were screened and 320 were randomized. The 223 people screened but not randomized presumably lacked active NRTIs. This study is very selective since it represents only the proportion of PI-experienced people who are more likely to achieve treatment success with a new regimen, given that they are receiving at least 3 active or partially active agents with the new regimen. It is highly unlikely that a majority would not achieve BLD, even though NNRTIs were not allowed. Thus, AAUCMB is a questionable measure of efficacy. This patient screening criteria was likely an important issue in the success rates observed. This study shows that 908/r is a potentially useful agent for second or third line PI therapy, but more data is needed.

At 48 weeks, non-inferiority of 908/r BID and 908/r QD compared to LPV/r BID could not be established. In other words, no go vs Kaletra®. Which is not fatal. Atazanavir was also just approved, even though it showed it was very inferior to Kaletra®.

4. Side effects

Contraindications

908 is contraindicated in patients with clinically significant hypersensitivity to the drug or any components in the formulation. Please see Appendix 1. What are the implications of administration of 908 with sulfa drugs?

Adverse Events/Toxicity

Early research by the sponsor suggested that amprenavir's unique chemical structure made it less likely than other protease inhibitors to disrupt lipid synthesis and hydrolysis (Lenhard et.al. posters 665, 666 from 6th CROI, 1999). Unfortunately, these results have not been confirmed.

Even though it is still a sulfa drug, rash is much lower with 908 than amprenavir. The reasons for this are not clear. Although most rashes with amprenavir are mild to moderate in intensity, approximately 1% of patients receiving it develop a severe or life threatening rash (Grade 3 or 4), including Stevens-Johnson syndrome. 908 should be discontinued in patients with severe or life threatening rash or with moderate rash accompanied by systemic reactions.

Body fat accumulation and redistribution (including increased fat in the upper back and neck, "buffalo hump", breast, around the trunk), loss of fat from the legs, arms, and face), hyperlipidemia, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus is often seen in patients receiving protease inhibitors.

Safety results NEAT	SOLO	Context		
	n=166	n=322	n=210	
Clinical (grades 2-4)	908BID	908/r	908/rQD	908/rBID
Diarrhea	8 (5%)	28 (9%)	5%	10%
Nausea	9 (5%)	21 (7%)	4%	3%
Vomiting	3 (2%)	19 (6%)	2%	2%
Rash	12 (7%)	5 (2%)	NR	NR
NR – not reported				
Metabolic parameters and blood analysis abnormalities (grades 3 and 4)				
ALT#	10 (6%)	25 (8%)	6%	4%
AST#	9 (6%)	19 (6%)	4%	4%
Triglycerides	0	16 (6%)	4%	8%
Cholesterol	0	1 (<1%)	0*	0*
Glucose	1 (<1%)	1 (<1%)	0	0

* - small lipid changes.

Context reported a high level of grade 2-4 “overall” side effects (908/r QD – 19%, 908/r BID – 35%, LPV/r – 34%. High withdrawal rates are the result (~30%). Lab abnormalities (grade 3-4) seemed equal across arms. There were more serum lipase elevations in the LPV arm vs the 908 arms.

Neat study		908 BID		NCEP Guidelines NFV BID		
	Mean values (mg/dL)	BL	Wk 48	Optimal/ Near Optimal range	BL	Wk 48
Lipids	Total cholesterol	152	197	< 200 mg/dL	153	203
	LDL Cholesterol	86	119	< 130 mg/dL	89	122
	HDL Cholesterol	37	49	> 40 mg/dL	36	44
	Triglycerides	151	152	< 150 mg/dL	154	200

The rate of GI side effects appears reduced with 908, although it was compared to NFV, famous for diarrhea (18% vs 5%, p = 0.002). Comparing it with historical data to Agenerase®, the GI issues are much less a concern. It is unclear why. The lipid changes were comparable for the 2 drugs.

Elevations in lipid values were observed in both groups, although triglycerides rose more for NFV BID at week 48. The overall incidence of drug related grade 2–4 adverse events was comparable.

In the Solo study (908/r QD), fasting triglycerides increased from mean levels of 147 mg/dL in 908/r patients to about 239 mg/dL at week 48, more than for NFV which reached the NCEP cut-off of 200 mg/dL. Fasting total cholesterol increased from 150 mg/dl to about 220 mg/dL at week 48. NCEP cut-off is 240 mg/dL. Fasting LDL (bad cholesterol): increased from 100 mg/dL to approximately 125 mg/dL at week 48. NCEP cut-off is 160 mg/dL. Regarding the proportion of patients with </> 40 mg/dL HDL cholesterol (the NCEP cut-off), 40% of those taking 908/r had >40 mg/dL at BL, which rose to 75% at week 48.

Food Interactions

High-fat meals should be avoided with Agenerase® because they may decrease the bioavailability of the drug. There is no such interaction issue with 908 use.

5. Resistance

The protease I50V mutation and others at positions 10, 20, 36, 73, 82, 90 were individually associated ($p < 0.2$) with a poor virological response to APV, in a univariate analysis. The P459Ins was significantly associated with a decreased virological response ($p=0.006$) and was more frequent when the V82A/F/T/I PR mutation was present ($p=0.02$). In a multivariate analysis, the impact of P459Ins remained significant ($p=0.057$) after adjustment for predictive factors of the virological response in the NARVAL, a French study, and on the PR mutations linked with response. These results suggest that insertions in the p6 region of HIV-1 gag gene can affect the virological response, in highly pretreated patients receiving an unboosted APV-containing regimen.

In the Neat and Solo studies, emergence of resistance was examined by ViroLogic via genotypic and phenotypic analyses of virus from all subjects with VL > 1000 c/ml at two consecutive visits between weeks 12 and the end of study.

In the Neat study, mutations characteristic of development of 908 resistance were detected in virus from 5/29 (17%) 908 treated subjects analyzed (3% subjects exposed) and included I54L/M, V32I + I47V and M46I. Mutations observed with other PIs (D30N, I54V, V82A/T/S, L90M) were not observed with 908. NFV-selected mutations (D30N, N88D/S, or L90M) were detected in 6/26 (23%) NFV-treated subjects analyzed (7% subjects exposed).

In the Solo study, no selection of PI resistance by 908/r was observed in virus from 31 subjects analyzed. Emergence of resistance with NFV was significantly greater ($p<0.001$) with D30N and/or L90M detected in 20/55 (36%) NFV-treated subjects analyzed. The absence of resistance selection at 48 weeks by 908/r indicates a high genetic barrier to resistance. Clearly, this is another reason to recommend its use only when boosted by /r.

The incidence of 3TC resistance (M184I/V) was significantly lower in 908/r-treated subjects (4/32 [13%] vs (30/55 [55%] $p<0.001$). Also, 0/32 patients taking 908/r had abacavir resistance (K65R, L74V) and 2/54 (6%) taking NFV had abacavir resistance (2 K65R, 1 L74V).

Resistance was evaluated at a time-point called “Last On-therapy Time Point": 0/11 patients taking 908/r QD had primary or secondary protease resistance mutations. 1 patient had the 3TC M184V mutation. 7 patients did not meet the original criteria for analysis (VL >1000 c/ml at 2 consecutive time points after being <400 c/ml) and 0/7 had primary and secondary protease mutations. 1/7 developed the 3TC mutation.

Hypersusceptibility

Hyper-susceptibility to amprenavir has been reported. The clinical significance of this remains unclear. ESS40006 was designed to compare 2 regimens of amprenavir (APV)/ritonavir (/r) (600/100 vs 900/100 twice daily) in subjects failing their current regimen. NNRTI-naïve subjects were also started on efavirenz, abacavir, and one additional NRTI, based on baseline susceptibility (abacavir >5-fold-change from control, all others =4, PhenoSense). NNRTI-experienced subjects received tenofovir in place of efavirenz. The effect of hyper-susceptibility to APV was assessed to identify predictors of virologic response at week 24 (< 200 c/mL). Baseline APV-fold change was used as a continuous variable and APV HS was defined as < 0.66 FC based on sample distribution.

After this elaborate study, the best that could be said is that hypersusceptibility may be a factor (along with lower baseline viral load) in achieving undetectability at 24 weeks in NNRTI-experienced subjects. The unexpected but much more clear finding of this study revealed that people on EFV did much worse as result of the interaction between the two (AMP and EFV) (see Drug/drug Interactions).

Cross Resistance

Novel early mutations to amprenavir may not confer cross-resistance to other PIs initially, but the subsequent accumulation of additional mutations confers broad cross-resistance to the entire protease inhibitor class.

908-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates do not show much although the drug has been around for 4 years! This is not acceptable.

CROI poster 598 (2003) suggests that 908 virologic failures are still susceptible to the gamut of PIs (no cross-resistance). Experience tells us that no matter how good the in vitro data, real life can't be beat. We do not know what 908 users switch to and how well the following therapy works if they are one of the ~30% of people in whom it fails.

6. Drug-drug interactions

Amprenavir is a substrate and moderately strong inhibitor of p4503A4, a hepatic enzyme that contributes to the metabolism of several other drugs. As a result, patients and clinicians need to be mindful of 908’s potentially serious drug interactions. There is a large and important list of interactions in Appendix 1.

Amprenavir had 1744 IU of vitamin E in the recommended daily dose. 908 does not contain vitamin E.

Drug-drug interactions with other antiretrovirals

Although amprenavir appears to be a less potent inhibitor of CYP3A4 than some other protease inhibitors, its metabolism is mediated by it to some degree. Drugs that induce isoenzyme CYP3A4 may reduce amprenavir plasma concentrations. Conversely, drugs that inhibit 3A4 may increase APV plasma concentrations.

	ddI	EFV	NVP*	DLV	SAQ	IND	NLF	KAL**
Does 908 cause								
Changes in								
Other ARVs?	ND	ND	ND	-61%	AUC –18%	-38%	+15%	-48%
					Cmin –46%	-27%	+14%	-61%

*With NVP, there is (sadly, 4 years later) no data.

**Results from A5143 were reflected in a poster at ICAAC 2003, saying that "908 + KAL does not appear to be a viable regimen in HIV-infected, treatment experienced patients". This lower exposure may put patients at risk of virologic failure, and therefore enrollment in A5143 was ended.

A PK study in 2000 suggested an adjustment in dosage or regimen when amprenavir is co-administered with didanosine. A more recent GSK study with buffered ddI and ddI EC lowered amprenavir levels by some 15% and 6% for EC. Amprenavir may be concurrently administered with both versions of ddI.

Monitoring drug concentrations and adjusting dose has been recommended for KAL and APV since January 2002, but the eight-week data from this study was just presented.

...and then there was Ritonavir

	Amprenavir AUC	Cmin	Change?
ddI	-15%	-6%	no change recommended
EFV	-36%	ND	boost with /r
NVP	ND	ND	why?
DLV	+130 – 400%	ND	do not use – why?
SAQ	-32%	ND	no change–why?
RIT	+250 – 350%	ND	Use – why?
IND	+33%	ND	no recommendation
NLF	+50%	ND	no recommendation
KAL	-63.5%	-69%	do not use

In Europe, amprenavir is licensed only for use with /r. The 908 docket from the sponsors is seeking the same (1400/200) at the EMEA now.

In Feb 2002, the FDA approved the combination Agenerase®/r. This combination was not recommended (although Agenerase® by itself was not recommended either). See reference above to the DHHS guidelines.

The Agenerase® package insert at the FDA was revised to include the following statement: If Agenerase® and ritonavir are used in combination, the recommended dosage regimens are: Agenerase® 1200 mg with ritonavir 200 mg once daily or Agenerase® 600 mg with ritonavir 100 mg twice daily. At the same time, the Precautions section was revised to provide additional information about possible cholesterol, triglyceride and liver transaminase elevations when amprenavir is co-administered with ritonavir. This section was also revised to provide information about the potential for lipid elevations. Guidance on monitoring and managing these clinical chemistry abnormalities was included.

7. What's unknown

Amprenavir is defined as a Class C antiretroviral for pregnancy; it has unknown placental passage (newborn: mother drug ratio), and four years after approval has not completed long-term animal carcinogenicity studies; for animal teratogen studies is negative (but deficient ossification and thymic elongation in rats and rabbits). We firmly believe that 908 should be studied and categorized for use in pregnant women.

Three ACTG studies were in place at the time of amprenavir's accelerated approval. 1 of those had to close because of important interaction issues, while another could not recruit. The final one has never been fully published. The community hopes that transparency and better definition be the hallmarks of all Phase IV studies, those already begun as well as those requested here (see Appendix 3).

The pediatric formulations need to be devised and studied in newborns and infants.

908/r vs atazanavir/r (QD) in different populations to help better define the use of 908/r in the real world.

Another study in advanced patients would be 908/r vs tipranavir/r vs LOP/r (all BID) would be very useful.

A PK assessment in people with different stages of hepatic impairment should be done.

What is the significance of the I50L and hypersusceptibility?

ACTG studies 5015 (accelerated disease and aging) and 5073 (a DOT study) are fully enrolled and should be reporting results soon.

8. Access

Expanded access with 908 has never been available. We would like to express our disappointment at the sponsor's not taking the opportunity to use this drug in real life circumstances before approval. Some form of EA would have helped to better define some of the outstanding real-life questions described in this paper, especially side effects, resistance and interactions.

ADAP funding is in jeopardy and Medicaid may be getting cut. If the sponsors are not willing to work with government/state programs, access to this new drug will be limited. However, the survival of people living with AIDS and the prevention of further HIV transmission requires that industry pursue market share through fair pricing. We urge GSK and Vertex to price 908 cost neutral with Kaletra® to afford the greatest number of people the option of using the drug.

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The following organizations and individuals have signed on to this paper along with Treatment Action Group:
[list in formation]

· AAPNW (AIDS Action Project Northwest), Portland, Oregon
· AIDS Action Baltimore
· AIDS Action Washington
· AIDS Treatment Data Network, New York, New York
· The Center for AIDS, Hope & Remembrance Project, Dallas, Texas
· CHAMP (Community HIV/AIDS Mobilization for Power), Philadelphia, Pennsylvania
· The Drug Development Committee of AIDS Treatment Activists Coalition, USA
· Gay Men's Health Crisis (GMHC), New York, New York
· HIV Advocacy Council of Oregon and SW Washington, Portland, Oregon
· IFARA (International Foundation for Alternative Research in AIDS), Portland, Oregon
· Positives For Positives, Cheyenne, Wyoming
· Program for Wellness Restoration, PoWeR, Texas
· Search for a Cure, Boston, Massachusetts
· Test Positively Aware Network, Chicago, Illinois
· Carlton Hogan, University of Minnesota
· Melvin Littles, New York, New York
· Robert J. Munk, Arroyo Seco, New Mexico

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APPENDICES

Appendix 1, Interactions with amprenavir. Will they be the same for 908?

Coadministration of amprenavir and methadone can decrease plasma levels of methadone. Dosage of methadone may need to be increased when co-administered. Coadministration as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, Cmax, and Cmin, respectively. Agenerase® may thus be less effective in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered. Note – the study was done two years after Agenerase® approval.

With oral contraceptives, there is a potential for metabolic interactions. An alternative method is recommended. Patients taking Agenerase® should not use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir, leading to a loss of virologic response. Patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with Agenerase®.

With sildenafil, the AUC increases 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects (the standard PI recommendation for sildenafil). Sildenafil-associated adverse effects, including hypotension, visual changes, and priapism, may be heightened.

Chemical properties of 908 suggested an interaction with antacids. In 26 non-HIV+ subjects, following single dose administration of 908, both Maalox and Zantac moderately reduced APV AUC_{last} and C_{max} when co-administered with 908, but neither reduced APV C_{12}. Increased gastric pH is the likely interaction mechanism. Based on the magnitude of the interactions seen, these results are unlikely to be of clinical significance when co-dosing 908 with either Maalox or Zantac.

There is a potential for a large increase in statin levels. Simvastatin and Lovastatin are to be avoided. A recent poster at ICAAC suggests that with or without /r, atorvastatin AUC rises by between 2.3 and 2.53 times. GSK suggests a smaller dose of atorvastatin or a different statin, including pravastatin for which there is no data. The increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.

Neither St John's Wort (Hypericum perforatum) which is expected to substantially decrease drug plasma levels nor echinacea should be used with Agenerase®. Garlic supplements and milk thistle should be used with caution.

The anti-tuberculosis drug rifampin should not be co-administered with amprenavir due to a decrease in the levels of APV by some 80%, and the dosage of rifabutin (MAC prophylactic) should be decreased – cut in half - when used with amprenavir (Polk et.al. abstract 340 from the Fifth Conference on Retroviruses and Opportunistic Infections 1998). Rifapentine should also be avoided.

Very serious effects can also result from co-administration of a number of other drugs including ergot alkaloids, the contraband Seldane, and sleep inducers Halcion and Versed. Serious or life threatening events can occur if amprenavir is taken with amiodarone, lidocaine, tricyclic antidepressants, and quinidine. Patients receiving amprenavir concomitantly with any of these drugs must be carefully monitored.

With ketoconazole, APV levels increase by 31%. Ketoconazole in the presence of APV increases some 44%. Dose adjustments are not considered necessary.

With voriconazole, there has been no data generated, but there does exist a potential for bi-directional inhibition between voriconazole and PIs. Toxicities should be monitored.

The antimycobacterial clarithromycin decreases amprenavir by 18%. No dose adjustment is called for.

With carbamazepine, phenobarbitol and phenytoin, interactions are unknown, but they may decrease amprenavir levels substantially. Monitor anticonvulsant levels.

This drug should not be used with the following medications because very serious interactions may occur: pimozide (an antipsychotic), and benzodiazepines (like midazolam and triazolam). Other drugs that are contraindicated with amprenavir include dihydroergotamine, methylergonovine, the calcium channel blocker bepridil, antihistemines astemizole andterfenadine, and the gastro-intestinal cisapride.

Although amprenavir is a sulfonamide, the potential of cross-reactivity between amprenavir and other sulfa drugs is unknown. 908 should be used with caution in patients with histories of sulfa allergies.

If amprenavir is coadministered with ritonavir, flecainide and propafenone (antiarrythmics) are also contraindicated.

Appendix 2, EAPs for amprenavir:

Protocol 30011 - This expanded access protocol was designed to determine whether adding a second protease inhibitor to a regimen containing amprenavir, abacavir and two RTI's improved treatment outcome in heavily pretreated patients. The choice of whether or not to use the second PI (and which second PI to employ) was left to the patient and his/her doctor. The trial was open to adults and adolescents over the age of 13 who failed at least one PI, had a CD4 count less than 400 and viral load greater than 10,000.

Protocol 30012 - This trial was established to determine whether patients suffering the effects of lipodystrophy syndrome and/or hyperlipidemia benefited from switching from their current PI to amprenavir. It was open to adults and adolescents > 13 years of age who were not failing their current regimen (defined as viral load < 10,000) but who were experiencing hyperlipidemia (abnormally high fat levels in the blood) with or without lipodystrophy. Concomitant use of another protease inhibitor was not permitted.

Protocol 30010 - This was similar to a traditional expanded access program, open to adults and children age 4 and above who failed or became intolerant to treatment with at least one protease inhibitor.

Appendix 3, ACTG 398:

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ACTG 398 assessed whether a 2nd PI, given with APV, ABC, EFV, and ADV would improve virologic response in 481 PI-experienced patients. Patients were selectively randomized, based on prior PI use, to one of four arms: SQV; IDV; NFV; or a 2nd PI placebo. At 24 and 48 weeks, the off-study rates were 6% and 12% and off-treatment rates for toxicity were 30% and 42%, respectively. The proportion reaching the primary study endpoint of virologic failure (HIV-1 RNA >200 c/mL) at 24 and 48 weeks were 69% and 79%, respectively. Virologic failure was significantly less frequent in the three dual-PI arms combined compared with placebo at week 24 (66% vs. 75%, p=0.03) but not at week 48 (77% vs. 82%, p=0.17). Virologic failure at weeks 24 and 48 was strongly associated with prior treatment with an NNRTI (p<0.001). Phenotypic drug susceptibility was determined in 139 subjects at baseline and in 64 subjects with virologic failure by week 24. EFV resistance predicted virologic failure at weeks 24 (p = 0.03) and 48 (p= 0.02). EFV hypersusceptibility protected against virologic failure at weeks 24 (p<0.001) and 48 (p< 0.001). Among virologic failures by week 24, resistance developed to EFV (p< 0.001) but not to other study drugs. Conclusions: Baseline EFV resistance and development of EFV resistance on study therapy were associated with virologic failure. Baseline EFV hypersusceptibility was strongly associated with better virologic response.

In ACTG 398, 25%(161) of subjects exhibited blips. CD4+ cell count increases at week 48 were no different between subjects who did and did not exhibit blips. Blips were not associated with virologic failure, and there was no association between baseline phenotypic sensitivity and blips (p=0.28). Failure to achieve HIV-1 RNA <50 c/mL in ACTG 398 was predictive of viral rebound (p<0.001).

Appendix 4, IQ:

atazanavir (ATV) 0.016±0.005;	ATV 400mg QD, 0.16 (0.11-0.21)	10.0, 9.4-10.6
indinavir (IDV) 0.071±0.028;	IDV/r 800/100mg BID, 0.99 (0.58-1.40)	13.9, na
lopinavir (LPV) 0.082±0.019;	LPV/r 800/200 QD, 2.46 (1.11-3.81)	30.1, 24.5-35.7
	LPV/r 400/100mg BID, 5.51 (4.22-6.80)	67.4, 54.9-79.8
nelfinavir (NFV) 0.761±0.159;	NFV 1250mg BID, 0.76 (0.61-0.92)	1.0, 0.7-1.3
saquinavir (SQV) 0.456±0.114;	SQV/r 1600/100mg QD, 0.61 (0.37-0.84)	1.3, 0.9-1.8
tipranavir (TPV) 4.7±0.8	TPV/r 500/200mg BID, 19.51 (0.43-42.83)	4.2, na

One of the objectives of pharmacokinetic/pharmacodynamic studies is to evaluate whether the three measures of systemic exposure, AUC, C max, or C min, correlate with a certain treatment response. Because AUC, C max and C min are strongly correlated with one another, drug response parameters (for example, decrease in viral load) that correlate with one of them will most likely also correlate with the other two. No study has directly compared Cmax, AUC and Cmin as predictors of treatment efficacy. Studies of virological efficacy have found a significant correlation between Cmin and AUC. The ratio of C min to IC50, defined as the 'inhibitory quotient' (IQ), is used by many researchers and is believed to be the parameter most likely to predict efficacy. Although still under debate, trough has correlated with outcome in a number of studies and it is the easiest to obtain in patients from a logistical standpoint. Additional data supporting the value of trough concentration for efficacy prediction have been generated using in vivo modeling approaches.

Dosage adjustment based on the IQ is widely thought to be a realistic goal. In the absence of inhibitory concentrations, viral mutants may be selected rapidly. The IC50 is almost invariably used as the denominator of the inhibitory quotient, although the fold increase in IC50 with respect to wild-type virus could be used as an alternative measure for adjusting dosages. IC90 or IC95 would be more logical parameters for a correct assessment of the inhibitory quotient, due to their closer association with the concept of viral escape from therapy. Nevertheless, they are not commonly used because these calculations are associated with a higher degree of error.

The optimal target may be a value of Cmin /IC50 greater than 1. The IQ value for a treatment-naive patient may be different from that needed for a highly treatment-experienced patient in order to achieve the same outcome. It is possible that patients who have failed a greater number of treatment regimens will harbor a higher number of viral subpopulations with a lower genetic barrier to resistance, which would need fewer mutations in order to become fully resistant. This may be true in spite of an apparently adequate Cmin /IC50, using the IC50 of the predominant viral species. Even treatment-naive patients may harbor a large number of mutant virus subpopulations in addition to the predominant viral species. Ideally, therefore, the IQ of all mutant viral variants that are present should be considered when predicting efficacy based on IQ.

Amprenavir inhibitory concentrations (IC50/Ctrough)

	AMP IC50
Wild type (n=334)	14.6 ng/ml μ 12.5
First time APV failure (n=36)	61.4 ng/ml μ 83.9
Multiple PI failure (n=328)	90.3ng/ml μ 84.6

	LOP/r or 908/r BID (n=8,8)	LOP/r+908 BID (n=17)	GM Ratio	p-value (upper 99.9% CI)
908 AUC_{12h}	41.77 (33.1-55.1)	15.2 (4.6-41.3)	0.36 (0.64)	<0.0001
908 C_{12h}	2.34 (1.42-3.2)	0.73 (0.2-2.7)	0.31 (0.61)	<0.0001
LPV AUC_{12h}	92.97 (60.3-119.3)	48.05 (23.5-112.2)	0.52 (0.89	0.0001
LPV C_{12h}	5.83 (2.2-9.2)	2.28 (0.4-7.9)	0.39 (0.98)	0.0008

908 and LPV/r exposure are significantly reduced when 908 and KAL are combined. Ritonavir exposure was similar in all arms. TDF did not account for the lowered PI exposures. This lower exposure may put patients at risk for virologic failure, and, therefore, enrollment in A5143 was ended. (A5143/A5147s protocol team letter to Protocol A5143/A5147s Participants, 8 August 2003).

Median	Min	Max	r^2 (p)
Cmin-ng/ml	1514	648	4981	0.03 (0.57)
Cminu-ng/ml	149	65	408	0.13 (0.25)
ICstd -ng/ml	57.8	8.7	150.9	0.67 (0.001)
IChs -ng/ml	452.2	33.2	1105.3	0.55 (0.006)
IQhs (Cmin/IChs)	3.6	1.3	43.8	0.31 (0.06)
IQu (Cminu/ICstd)	2.5	0.4	37.3	0.45 (0.02)
IQgen (Cmin/nb mutations)	309.8	90.6	1472.0	0.66 (0.001)

ICstd and IQgen were the best predictors of virological response to APVr.

A5143 was designed to evaluate the combination of 908+LPV/R, compared to 908/R alone or LPV/R alone with tenofovir (TDF)+1-2 NRTIs, in treatment-experienced patients. The lack of drug interaction data prompted an open-label, steady-state PK substudy to minimize subject risk. A planned independent interim review occurred after the first eight subjects were randomized to each arm. Arm A (n=8); LPV/R 3caps BID: Arm B (n=8); 908/R 700mg/100mg BID: and Arm C (n=17); LPV/R 3caps BID + 908 700mg BID. PK sampling (eight samples over 12h) occurred around observed doses at week 2-4 in the 33 subjects, 29 male, 21 white, with median age of 42y.