

## Reported Incidence and Severity of Suspected Abacavir Hypersensitivity Reactions (HSR) through at least 6 Weeks in a Large, Controlled Clinical Trial Using a Once-Daily (OAD) abacavir 600mg/lamivudine 300mg tablet (ABC/3TC FDC) Dual Nucleoside Backbone with a Boosted Protease Inhibitor: The KLEAN Study

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### Introduction

ABC and 3TC are potent nucleoside reverse transcriptase inhibitors that have been combined into one fixed-dose combination tablet given once-daily (EPZICOM™/ KIVEXA™, EPZ) for use as an NRTI backbone in HAART regimens. Both are generally well tolerated by most HIV-infected individuals, although a hypersensitivity reaction (HSR) has been reported in approximately 5% of subjects treated with ABC in controlled clinical studies.<sup>1</sup> Most cases of ABC HSR (>90%) occurred in the first 6 weeks of initiating ABC treatment, with a median time to onset of 9 days.<sup>2</sup> Data from >9,000 subjects in 37 clinical trials to date using ABC both OAD and BID yielded an overall rate of ABC HSR of 5.4% (range 0-14%) and demonstrated that the frequency of ABC administration (BID vs. QD) was not a risk factor for ABC HSR.<sup>3</sup>

KLEAN (ESS100732) is a large, open-label, multicenter, international study designed to compare the efficacy and safety of fosamprenavir 700mg BID + ritonavir 100mg BID to lopinavir/ritonavir 400mg/100mg BID, both administered in combination with an NRTI backbone consisting of EPZ OAD over 48 weeks in ART-naïve patients. KLEAN provides the largest cohort to date to assess the incidence and severity of ABC HSR with EPZ.

### Methods

Phase IIIB, open-label, randomized (1:1), multicenter, international study at 130 outpatient sites. HIV-infected adults were eligible for enrollment if they were antiretroviral naïve, or had limited experience (≤14 days NRTI experience, with no prior NNRTI or PI use), ≥18 years of age with HIV-1 RNA >1,000 copies/mL and any CD4+ cell count at screening. Subjects who experienced ABC HSR were allowed to substitute another NRTI and continue in the study.

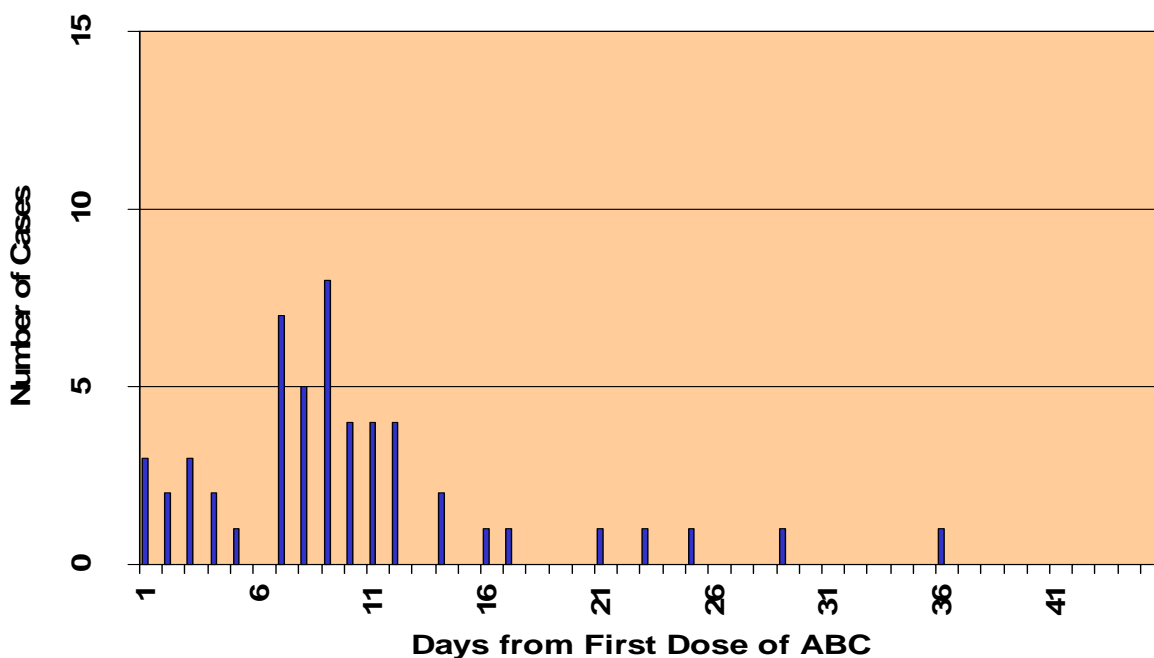
This is an unplanned, interim, non-comparative analysis of all subjects with at least 6 weeks exposure to EPZ. Descriptive results are presented from the GSK Safety Database with a cut-off date of February 18, 2005. Any cases of ABC HSR which occur after February 18, 2005 will be reported with the final study analyses.

Data on the rates of HSR between treatment groups is not presented in this analysis as this study is ongoing and no statistical comparisons are made. For this analysis, baseline was considered study day 0.

## Results

887 subjects enrolled in the KLEAN study between June 3, 2004 and January 7, 2005 from 130 sites in the US, Austria, Belgium, France, Germany, Italy, Latvia, Poland, Portugal, Spain and Switzerland. The data cut-off date of February 18, 2005 assured that all subjects had been on study for a minimum of 6 weeks (maximum of 37 weeks). Suspected ABC HSR was reported in 52 subjects (5.9%) as of the cut-off date. The median time to onset of these cases was 8 days (range 0-35 days) as seen in Figure 1.

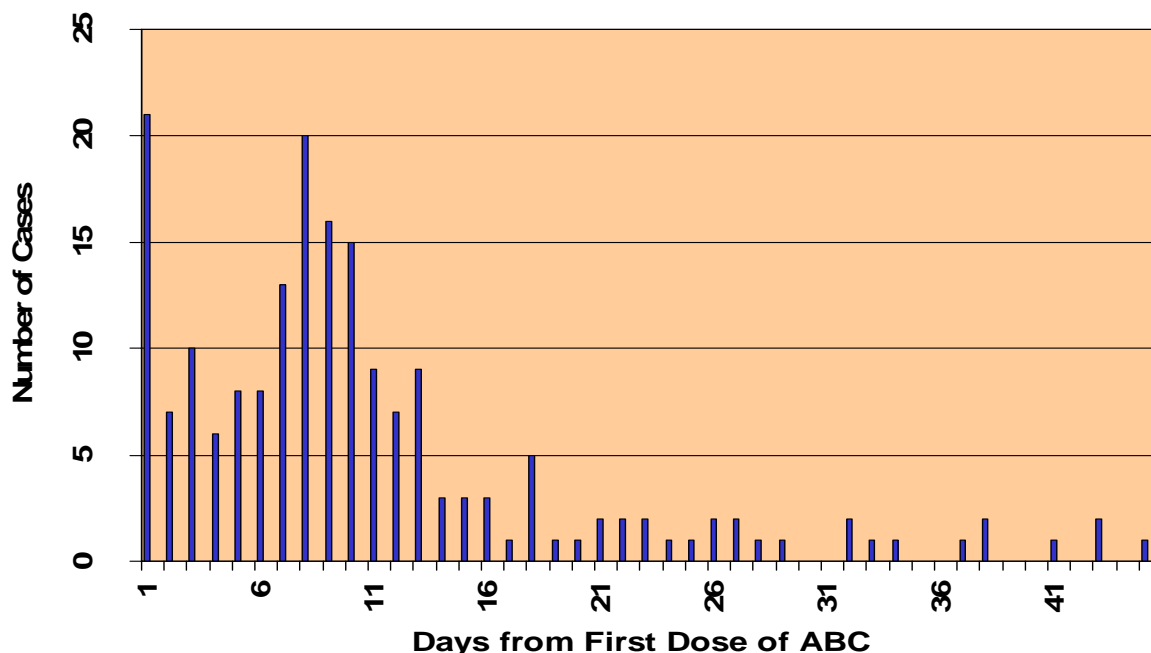
*Figure 1. Time to Onset of HSR Cases in KLEAN\**



\*Baseline was defined as Day 1 in figure 1 for consistency with historical data presented in Figure 2.

Figure 2 is a histogram of ABC HSR cases by time to onset in 9 recently reported studies using ABC. In this group of studies, the median time to onset of ABC symptoms was 9 days (range 1-384 days).

Figure 2. Time to Onset of HSR Cases in Recent Studies<sup>2</sup>



HSR was graded based on clinical judgment by the reporting investigator. In KLEAN, 8 cases (0.1%) were reported as Grade 1, 24 cases (2.7%) as Grade 2, 18 (2%) as Grade 3 or 4 while 2 cases did not have grading assigned as of the cut-off date. Hospitalizations were reported with 12 cases (1.4%), however these have not been confirmed as being related to HSR.

No cases of ABC HSR were fatal. Table 1 compares the reported rate and severity of ABC HSR cases in KLEAN (as of the cut-off date) to other studies using ABC OAD in subjects naïve to ABC.

Table 1. Reported Rates and Severity of HSR Cases in Studies Using ABC OAD

Study and No. of Patients	Suspected ABC HSR	Grade 3 or 4 ABC HSR	Hospitalizations	Deaths due to ABC HSR
CNA30021 (n=384)	39 (9.4%)	19 (4.9%)	5 (1.3%)	0
CAL30001 (n=93)	8 (8.6%)	4 (4.3%)	0	0
ESS30009 (n=340)	23 (6.7%)	9 (2.7%)	0	0
COL40263 (n=123)	8 (6.5%)	4 (3.3%)	0	0
<b>KLEAN (n=887)</b>	<b>52 (5.9%)</b>	<b>18 (2.0%)</b>	<b>12 (1.4%)</b>	<b>0</b>

## Discussion

- Preliminary data reported here from the KLEAN study are from an unplanned, interim, non-comparative analysis with all subjects through at least 6 weeks of therapy with EPZ. Additional cases of ABC HSR may be reported in this ongoing study. Since all patients had been through the period of highest risk, however, this dataset provided the opportunity to assess the incidence and severity of HSR with the use of EPZ.
- KLEAN is the largest controlled study of EPZ to date to assess the rate and severity of ABC HSR when ABC is dosed once-daily.
- KLEAN used the ABC HSR CRF module, which has been reported as a significant predictor for HSR reporting, likely a surrogate maker for the more conservative approach to diagnosis, management and reporting of HSR used in recent studies.<sup>3</sup>
- Importantly, there is no toxicity scale for grading ABC HSR, therefore variability in assigning grade is anticipated based upon clinical judgment and experience. This is likely confounded by the fact that all cases of suspected HSR in recent clinical trials are reported as SAEs regardless of whether they fulfill the NIOS<sup>4</sup> criteria of seriousness or not.
- This analysis confirms the findings of previous research showing that the use of ABC dosed once-daily is not associated with a higher rate or more severe presentation of HSR than when ABC is dosed twice-daily.<sup>2</sup>
- Finally, in this study, EPZ was dosed with a boosted PI, which may have some overlap in AE profile with ABC HSR (namely GI symptoms and rash). This could have led to an elevated rate of suspected ABC HSR, as has been demonstrated in the control arms of blinded studies using indinavir or zidovudine as the comparative agents.<sup>5</sup>

## Conclusion

- **The incidence of ABC HSR in this interim analysis of the KLEAN study (5.9%) is consistent with previously published data on the rate of HSR with ABC dosed once- or twice-daily.**
- **Consistent with previous data, the median time to onset of symptoms of ABC HSR in the KLEAN study was 8 days.**
- **The rate of severe (Grade 3 or 4) ABC HSR was low (2%) and similar to previously reported data for ABC 300mg BID and 600 mg OAD.**

## References

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