



Hepatitis C

HCCAP

October 1, 2006

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Antiviral Drugs Advisory Committee Meeting – Development of Products for Treatment of Chronic Hepatitis C

Dear Advisory Committee Members,

The Hepatitis C Caring Ambassadors Program, a national nonprofit hepatitis C advocacy organization, respectfully submits the following comments and suggestions, which represent our current position with respect to the clinical development of products for the treatment of chronic hepatitis C. Comments are presented in accordance with the stated issues to be discussed at the upcoming meeting on October 19 and 20, 2006.

Identification of Appropriate Control Arms

I. Therapeutic Exploratory Trials (Phase II)

In cases where an experimental therapeutic is being tested in combination with other therapeutics, we strongly advocate for the use of at least a two-arm, parallel comparison design (active control group) with rigorous matching and randomization protocols. Randomization protocols should be designed such that breaches of randomization are minimized. Matching procedures should take into account known potential confounders to optimize the probability of detecting therapeutic efficacy, should it exist, and to prevent erroneous exclusion of the same.

In accordance with Article 29 of the Helsinki Declaration of 2004, we advocate for rigor in ensuring that optimal standard-of-care is delivered to all patients in both the experimental and control arms of therapeutic exploratory trials. To that end, we urge that all trial protocols address not only the dosage and administration of the therapeutics under primary consideration, but also specify state-of-the-art monitoring for and

management of both major and minor adverse events to ensure that all participants' chances for therapeutic response are optimized.

In cases of stand-alone experimental therapeutics, we again advocate for a parallel comparison design (active control group) with rigorous matching and randomization protocols. While this design is more complex (and costly) than a baseline-controlled design, we believe the serious and potentially life-threatening nature of chronic hepatitis C necessitates this approach and optimizes the efficacy of the study by providing comparative data (to standard-of-care) on which to base the decision about whether phase III testing is advisable. Due to treatment-trial confounding, we recommend against the use of historical controls in this setting.

In instances where experimental therapeutics designed to attenuate disease progression (without the intent to clear virus) are being evaluated, a baseline-controlled study design may be appropriate. However, these decisions should be made on a case-by-case basis.

Finally, we advocate that all therapeutic exploratory trials be designed with specific stop-points based on the best currently available data. Interval analysis and predetermined stop-points help maximize patient safety and minimize imprudent use of limited resources.

II. Therapeutic Confirmatory Trials

We advocate that all therapeutic confirmatory trials be randomized, blinded, and controlled with an active control arm design. In trials with multiple experimental arms, we advocate for fixed concentration window design over fixed dose design, unless clear and reliable evidence exists that supports the integrity of the latter.

Our recommendations with respect to matching, randomization, and trial protocol specificity (especially with regard to adverse event management) are as for therapeutic exploratory trials.

Populations for Study

I. Pharmacokinetic and Pharmacodynamic Studies

Studies involving the pharmacology of an investigational therapeutic should include a representative sample of the populations most burdened

(as measured by prevalence data) by chronic hepatitis C. The demographic factors most likely to be associated with significant genotypic variability in host systems believed to be part of the mechanism of action, activation, detoxification, and/or elimination of the investigational compound should be specifically considered and addressed in the study design with respect to defining the study population. In general, we advocate that pharmacologic studies should strive for inclusion over exclusion. Although this recommendation may initially appear to be inconsistent with commonly-held notions about the relatively small size of phase I studies, we believe that the identification of relevant differences in pharmacologic studies ultimately leads to more appropriately designed and efficacious therapeutic exploratory and confirmatory trials. Specifically, we advocate for the inclusion of equal numbers of males and females, and racial diversity to include Caucasians, African-Americans, those of Hispanic descent, and those of Asian descent in adequate numbers to assess potential differences in pharmacologic response due to genotypic host variability.

While we understand the advantage and relative necessity of conducting first-line pharmacologic studies in people without significant co-morbidities, we advocate for conducting similar studies in the HIV-HCV coinfecting population as soon as possible for investigational agents advancing from pharmacologic study to therapeutic exploration. The high prevalence of HCV coinfection in the HIV-infected population and the increased relative risk of disease progression mandate special attention and rapid development of therapeutics for this subpopulation of patients at particularly high risk for severe morbidity and high rates of mortality due to chronic hepatitis C. Pharmacologic data specific to this population is required because of the added complexity introduced by the immune status of these clients and the risk of interactions between investigational agents and standard HIV anti-virals.

II. Therapeutic Exploratory Trials

We are well aware that there is an inversely operational balance to be struck between adequately powering a phase II trial to detect potential efficacy and the relative inclusionary/exclusionary nature of the criteria that defines the study population. A study design that introduces too many confounders for the size of the study population has an increased likelihood of type II error. A false negative conclusion drawn in a phase II trial has the potential to be a catastrophic loss to the population of persons living with chronic hepatitis C, and therefore must be guarded against.

Recognizing the challenges posed in designing feasible, statistically sound phase II trials, we strongly advocate that the FDA develop specific guidelines to help those designing and executing therapeutic exploratory trials balance the competing parameters of adequate statistical power and the applicability/generalizability of the study findings. We suggest the guidelines be structured such that they can be applied on a case-by-case basis during the design stage of a trial to help investigators decide upon an evidence-based rationale to minimize the probability of type II error and maximize applicability/generalizability of the study findings.

III. Therapeutic Confirmatory Trials

We urge the FDA to require that phase III registration trials be as inclusive as possible (with respect to the defined study population) without jeopardizing the statistical power of the trial. Given that an investigational agent that has reached phase III testing is a de facto candidate for use in the general population of persons afflicted with chronic hepatitis C, we recommend that such studies be conducted in study populations designed to be representative of those populations most heavily burdened by the disease (as evidenced by prevalence data). Specifically, we recommend that such trails be designed to be equally representative of both males and females, that the age distribution of the study population mirror the relative burden of the disease in specific age groups, and that racial diversity be addressed in the recruiting and matching and randomization protocols.

Acknowledging that a study design that fails to control for potentially significant confounders in the study population cannot feasibly be adequately powered to provide to clinically useful data, our recommendation must be considered in context. We do not advocate for studies that sacrifice the potential for sound findings in exchange for excessively broad inclusion criteria. Nor do we advocate for studies with such broad inclusion criteria as to inordinately prolong the clinical trail and potential approval process to such extremes as to limit access to a broader population base. As mentioned with respect to therapeutic exploratory trials, there is a balance to be struck. We urge the FDA to develop guidelines to assist investigators in making these complex, but crucially important design questions.

Finally, recognizing that in some instances, specific special populations may, of necessity, be excluded from phase III registration trials because of statistical, logistical, and practical constraints, we urge the FDA to work with therapeutic developers and manufacturers to ensure that the specific needs of those populations excluded from registration trials are addressed quickly in additional therapeutic confirmatory and use trials as a condition of approval.

Clinical Trial Endpoints (Outcome Measures)

In general, the professional hepatology community has explored and developed this area based on their extensive knowledge and experience. Further, it is our

opinion that most chronic hepatitis C registration trials to date have been well-designed with respect to outcome measures and endpoints.

Nonetheless, there is always room for improvement, especially in the rapidly shifting environment of chronic hepatitis C therapeutics. We put forth our recommendations regarding chronic hepatitis C clinical trial endpoints in the following paragraphs.

I. Anti-fibrotic and anticarcinogenic effects of hepatitis C therapeutics

Previous clinical trials and retrospective studies suggest interferon-based therapy may slow chronic hepatitis C disease progression and reduce the risk of the development of hepatocellular carcinoma (HCC) even among patients who fail to clear virus. This is a potentially important therapeutic topic to explore with the objective of arriving at conclusive data. We urge the FDA to encourage exploration of this important possible indication for continuation of interferon-based therapies in those who do not achieve early viral response (EVR). This could be done by providing options for clinical trial participants at designated stop-points in therapeutic confirmatory studies. Even without viral clearance, if definitive evidence showed a significant protective effect, such use of therapeutics may well prove to be a cost-effective intervention.

II. Monitoring for hepatitis C viral clearance

Evidence exists suggesting that use of whole blood (rather than plasma or serum) leads to increased sensitivity when monitoring patients for hepatitis C viral clearance. We urge the FDA to encourage trial sponsors to make use of this laboratory tool in monitoring for HCV clearance with respect to new anti-viral therapeutics for chronic hepatitis C. Parallel testing of plasma/serum and whole blood samples would be ideal.

Collaboration between registration trial sponsors and device manufacturers for such purposes should be encouraged.

In cases where whole blood testing is not used in a therapeutic trial, we encourage the FDA to require sponsors to use HCV quantitative assays with optimal sensitivity and specificity for viral load and clearance monitoring. Further, we encourage FDA (in collaboration with other comparable national/regional agencies) to develop a minimum requirement with respect to these parameters for all chronic hepatitis C therapeutic trials.

III. Early viral response

HCV study data increasingly support the notion that for interferon-based therapies, early response is predictive of sustained viral response. While current practice indicates a 12-week decision point, evidence is mounting that earlier time points may be of equal or greater importance.

We urge FDA to encourage chronic hepatitis C trial sponsors to include viral response monitoring at early time points (i.e., at least week 1, week 4, and week 8) and not just as required according to stop point rules (typically week 12).

IV. Targeted therapies

Given that the focus in the arena of development of new therapeutics for chronic hepatitis C is on targeted anti-viral agents, it is important that rigorous monitoring for the development of resistance is incorporated into the trial design for such agents. We urge the FDA to require such monitoring with timely interim analysis and predetermined management rules for patients who develop resistance. The specifics of such requirements will need to be considered on a case-by-case basis until such time as sufficient evidence is accumulated to potentially develop guidelines in this area.

V. Adverse events

Detailed adverse events (AE) monitoring and reporting are crucially important aspects of all therapeutic exploratory, confirmatory, and use trials. While adverse event monitoring is not necessarily the primary outcome measure in many trials, this does not diminish its importance.

We encourage the FDA to develop specific, detailed tools that standardize and expand upon currently used adverse events monitoring for chronic hepatitis C clinical trials. The AE monitoring tool should be detailed such that those evaluating study data are able to easily understand exactly what types of AEs have occurred. For example, reporting “gastrointestinal” as a category of AE tells little about the actual events experienced in the trial. We recommend the development and use of a standardized, detailed categorization that would communicate the specific nature and severity of AEs. For illustrative purposes only (and not intended to be exhaustive), an example is shown below:

Gastrointestinal AE

A. Minor

1. anorexia
2. dysgusia
3. dyspepsia
4. intermittent abdominal pain
5. intermittent diarrhea
6. unintentional weight loss, BMI in normal or above

range

7. intermittent constipation

B. Major

1. pancreatitis
2. variceal bleed

3. unintentional weight loss resulting in drop of BMI to “underweight”

We urge the FDA (to the extent allowed under the legal powers granted to the agency) to not only develop but require use of detailed AE monitoring and reporting (i.e., publicly available data) for all chronic hepatitis C therapeutic trials.

VI. Quality of life indicators

The tolerability of therapeutics for chronic hepatitis C has become an issue of great concern in the hepatitis C community. In accordance with the old adage, “No news is good news.”, a perception has emerged in the community of people living with hepatitis C that therapeutics for the disease are in many ways “worse” than living with the disease itself. While this may seem to be a relatively insignificant (albeit unfortunate) situation, the implications are quite serious when one considers the level of fear and avoidance that many for whom therapeutic intervention is clearly indicated experience, and for whom this same belief may cause a decision to defer treatment that could potentially reverse a life-threatening situation.

Therefore, we urge the FDA to encourage (if not require) all sponsors of therapeutic hepatitis C trials to not only monitor for AEs, but also to collect information regarding quality of life and performance status (using standardized data collection tools). It is well understood that the tolerability of hepatitis C therapeutics is highly variable; it is also clear listening to the constituents of the hepatitis C advocacy community that the only experiences “with legs” are the worst case scenarios. While it is true that some people have substantial difficulty tolerating treatment (and experience undeniable suffering as a result), it is also equally true that this is far from a universal experience.

It is imperative that reliable data be collected and reported on the day-to-day tolerability of HCV therapeutics so that objectivity can be introduced to mitigate the inordinately negatively skewed view of treatment that causes many who need treatment to avoid it.

Long-Term Follow-Up for HCV Clinical Trials

I. Post-Hepatitis Syndrome

Some investigators have proposed an ongoing clinical entity dubbed, “post-hepatitis syndrome” to describe a constellation of largely constitutional symptoms (somewhat vaguely defined at this juncture) that persist after viral clearance and negatively affect quality of life and productivity.

To the extent possible, we urge the FDA to encourage chronic hepatitis C trial sponsors to collect data during and for at least two years after the active phase of therapeutic trials to verify the existence of this entity, and assuming it occurs, to further define and quantify the incidence of this clinical entity.

II. Hepatocellular carcinoma

We urge the FDA to encourage long-term follow-up of chronic hepatitis C registration trial participants to determine the effect (if any) of chronic hepatitis C therapeutics on the relative risk of the development of hepatocellular carcinoma.

Additional Comments on Chronic Hepatitis C Clinical Trials

I. Funding

We encourage the FDA to work with the hepatitis C advocacy community to encourage increased federal support (through the National Institutes of Health) for non-industry sponsored chronic hepatitis C clinical trials.

II. Public reporting of negative clinical trial findings

We urge the FDA to work by whatever means possible to support the imperative that so-called “negative” trial data are made available to the health care community. Negative trial data are vitally important in the research and development, the evolving understanding of disease, and the implementation of good clinical care that first “does no harm.” We hold that this is an unequivocal truth for all patients, not just those with chronic hepatitis C.

III. Clinical trial protocol access

We urge the FDA to require that detailed clinical trial protocols be made available and easily accessible for all registration trials. Interpretation of clinical trial data is incomplete and insufficient without a detailed understanding of exactly what was done in the trial.

IV. Data collection on possible confounders

We urge the FDA to encourage the incorporation of the collection of data on possible confounders in all chronic hepatitis C clinical trial designs. At present, we posit that HCV clinical trials should collect data on (but not limited to) all participants’:

- height, weight, and BMI
- current smoking status
- current and past alcohol use
- current use of cannabis, hashish, or cannabinoids

- comorbidities
- concurrent medications
- activity level (at least semi-quantitative)
- performance status
- pretreatment [and interim] depression assessment (standardized)
- pretreatment [and interim] anxiety assessment (standardized)
- past history of mental health issues
- past history of immunomodulated conditions

In addition, we believe a detailed clinical history and pre-trial laboratory assessment is required, which should include screening for previously undiagnosed conditions that may be exacerbated by interferon-based therapy including (but not necessarily limited to) abnormalities of glucose regulation, undiagnosed renal impairment, and thyroid function.

Conclusion

The Hepatitis C Caring Ambassadors Program thanks the FDA for this opportunity to offer our comments and suggestions, and would welcome the opportunity to participate in the ongoing dialogue with the FDA and other stakeholders about this important issue.

Respectfully Submitted,

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