International Conference on Harmonization (ICH) Public Meeting

October 21, 2008, Rockville MD

Alcon Written Comments for Consideration by the Food and Drug Administration

Alcon would like the following comments considered and seeks Agency support for these changes to the ICH Harmonized Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

Current Text: Page 4, Table 1.

Duration of clinical trial	**Minimum duration of repeated dose toxicity studies.**	
	Rodents	**Non-rodents**
Up to 2 weeks	2 weeks[a]	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
> 6 months	6 months	9 months[b,c,d]

Proposed Text: Add footnote (*) from as follows:

Duration of clinical trial	**Minimum duration of repeated dose toxicity studies.**	
	Rodents	**Non-rodents**
Up to 2 weeks	2 weeks[a*]	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
> 6 months	6 months	9 months[b,c,d]

*** In the US, as an alternative to 2 week studies, single dose toxicity studies with extended examinations can support single-dose human trials.**

Rationale for Proposed Change:

In the M3(R1) Guidance, a single dose clinical trial could be supported with a single dose rodent study with extended examinations and a two-week repeated dose non-rodent study. This option is of benefit when a single dose clinical trial by a different route of administration (i.e., intravenous exposure for a topical ocular indication) is required to evaluate specific endpoints (bioavailability, cardiovascular safety, etc.). Additionally, M3(R2) Table 1

appears to be inconsistent with the approach described in Section 8 (Local Tolerance) where a local tolerance study in a single species is considered appropriate.

Current Text: Clinical Trials in Pediatric Populations, p 16, 7th paragraph

There can be cases where a pediatric population is the primary population; existing animal studies do not adequately address developmental concerns for target organs, and long term juvenile toxicity testing in a non-rodent would be valuable. In this case, a study initiated in the appropriate age and species of juvenile animals that covers the development period of concern can be appropriate. A non-rodent chronic study (e.g., 12 months duration in a dog to cover the full development period in this species) combining the objectives of the standard chronic and separate juvenile animal toxicity study can be appropriate.

Proposed Text (in bold):

There can be cases where a pediatric population is the primary population; existing animal studies do not adequately address developmental concerns for target organs, and long term juvenile toxicity testing in a non-rodent would be valuable. In this case, a study initiated in the appropriate age and species of juvenile animals that covers the development period of concern can be appropriate. A non-rodent chronic study (e.g., 12 months duration in a dog **that is approximately 6-8 weeks of age** to cover the full development period in this species) combining the objectives of the standard chronic and separate juvenile animal toxicity study can be appropriate.

Rationale for Proposed Change:

Clarification on the appropriate age range of the test species would help in study design. The weaning age of dogs is around 3-5 weeks, this time period would allow the dog to have a normal weaning cycle and allow its gastrointestinal system to adjust to normal dog chow.

Current Text: Section 7, Page 6, 1st paragraph

It is recognized that in some cases insight on human physiology/pharmacology, knowledge of drug candidate characteristics and therapeutic target relevance to disease are benefited by earlier access to human data. Streamlined early exploratory approaches can accomplish this end. Exploratory clinical studies for the purpose of this guidance are those intended to be

conducted early in Phase 1, involve limited human exposure, have no therapeutic or diagnostic intent, and are not intended to examine maximum tolerated dose. They can also be used to investigate a variety of parameters such as pharmacokinetics, pharmacodynamics and other biomarkers, which could include PET receptor binding and displacement.

Proposed Text (change in bold):

It is recognized that in some cases insight on human physiology/pharmacology, knowledge of drug candidate characteristics and therapeutic target relevance to disease are benefited by earlier access to human data. Streamlined early exploratory approaches can accomplish this end. Exploratory clinical studies for the purpose of this guidance are those intended to be conducted early in Phase 1, involve limited human exposure~~**, have no therapeutic or diagnostic intent,**~~ and are not intended to examine maximum tolerated dose. They can ~~also~~ be used to investigate a variety of parameters such as pharmacokinetics, pharmacodynamics and other biomarkers, **diagnostic measures,** or ~~**which could include**~~ PET receptor binding and displacement.

Rationale for Proposed Change:

For ophthalmic indications, biomicroscopic slit-lamp and fundoscopic examinations, changes in intraocular pressure (by pneumatonometer) or retinal thickness (by optical coherence tomography) are critical efficacy endpoints that may be observable from topical ocular dosing when the systemic exposure is $\leq 1/100^{th}$ of the NOAEL. Alternatively, a critical biomarker from tear film, blood or urine may be useful in determining efficacy or validating an animal model.

Current Text: Table 3. Doses to be administered

Approach 1: Total dose $\leq 1/100^{th}$ NOAEL and $\leq 1/100^{th}$ pharmacologically active dose.

Approach 2: each dose $< 1/100^{th}$ of the NOAEL and < 1/100th pharmacologically active dose.

Proposed Text:

Approach 1: Total dose $\leq 1/100^{th}$ NOAEL (**as determined by systemic exposure)** and $1/100^{th}$ pharmacologically active dose.

Approach 2: each dose < 1/100th of the NOAEL (**as determined by systemic exposure)** and < 1/100th pharmacologically active dose.

Rationale for Proposed Change:

For ophthalmic products, it is often not feasible to establish 100x the local clinical exposure based on formulation characteristics (i.e., solubility, osmolality, pH etc). Provided adequate systemic safety is established as described in the document and local (e.g. topical ocular) safety is established, it is proposed that the NOAEL is based on systemic exposure only.

Current Text: Page 10, Table 3, second statement under Pharmacology

Currently reads "Core battery of safety pharmacology"

Proposed Text:

Change to "Core battery of safety pharmacology studies"

Rationale for Proposed Change:

Incomplete statement

Current Text: Page 12, Table 3, second paragraph under Start and Max Doses

Currently reads "…should not be higher than the AUC at NOAEL in the Non-rodent species or than 1/2 the AUC…."

Proposed Text:

Change to "…should not be higher than the AUC at NOAEL in the Non-rodent species or higher than 1/2 the AUC…."

Rationale for Proposed Change:

For clarity

Current Text: Page 12, Table 3, statement under Pharmacology.

Currently reads "Core battery of safety pharmacology.

Proposed Text:

Incomplete statement

Rationale for Proposed Change:

Change to "Core battery of safety pharmacology studies"