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CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

ELECTRONICALLY REPRINTED FROM OCTOBER/NOVEMBER 2014

Blood Pressure Evaluation During Early Phase Trials

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A systematic approach for early identification of BP effects during development of new drugs.

More attention is being paid to blood pressure (BP) effects in new chemical entities under development for non-hypertension indications, especially when these are not anticipated and not thoroughly defined during drug development. Concern by scientists, clinicians, and regulators centers around small-to-moderate effects that can contribute to cardiotoxicity in a therapy otherwise thought to have none. Scientific and regulatory efforts to raise awareness and better define approaches to assessment of BP during drug development were presented in a report published in March 2013 by the Cardiovascular Safety Research Consortium (CSRC), a collaboration between the FDA and multiple academic and drug development experts.[1] While comprehensive in presenting the scope of the challenge and in providing an overall approach to evaluation of BP, specific proposals for the design of clinical trials were not made.

This article presents a plan for a systematic approach to identifying BP effects during typical Phase I and Phase II trials. Most compounds will be able to be studied using this approach without additional dedicated trials and without additional subject enrollment. The outcome of this approach would likely not definitively exclude a small BP effect but, rather, would identify the presence of an important BP effect sufficiently early in drug development to define the need for additional testing.

Justification for improved BP assessment

In general, it has been difficult to document the relationships between BP changes and cardiovascular (CV) events, particularly if these BP changes are modest in extent or occur only in a small proportion of treated patients. Clearly, a greater concern will exist with drugs that are intended to be administered chronically rather than for short term or occasional use. But beyond considerations for individual patients, there exists a public health issue: based on epidemiologic data, it can be argued that even small BP changes—if occurring in large cohorts of treated patients—might increase CV events across a community even if conventional safety studies do not detect an increased risk.

There are many issues to be considered in defining potentially adverse BP effects of drugs used for non-hypertension indications. If BP increases are observed, are they likely to cause major CV events? Or are the increases a biomarker of some other mechanisms that could cause CV outcomes? For instance, non-steroidal anti-inflammatory drugs can cause increases in BP and are also associated with increased CV events. But it is not clear whether these increased event rates are due to the underlying disease (arthritis has been linked to increased CV risk), to the potential pro-thrombotic effects of these agents, or to the observed increase in BP.[2]

Another example is the increased mortality observed with the anti-obesity agent, sibutramine.

Even though there was an increase in BP in the definitive CV outcomes trial, SCOUT,[3] that evaluated this agent, there was no evidence that patients with fatal events while taking this drug actually had increases in BP, compelling the investigators to speculate that other mechanisms were responsible. Perhaps the best direct evidence for BP elevations causing events has been with the vascular endothelial growth factor inhibitors used in cancer therapy: the sharp increases in BP that can be produced by these agents appear to have a direct connection to stroke events.[4]

Systematic evaluation of blood pressure effects: A working checklist

From the perspective of adverse BP events, a checklist of questions, previously presented by one of the authors,[5] can be applied to new drug development. The proposal in this article can reasonably only address questions 1 though 7 in the following list and summary, but allowing these to be defined will greatly aid in decisions for answering the others.

1. Do BP increases actually occur? A direct BP-raising effect may occur almost immediately while the drug is in the circulation and thus could be readily detected in standard Phase I trials or after a short period of repeated dosing, as in a Phase II trial.

2. What is the incidence of this effect? In most cases, this calculation can best be determined during Phase II. For drugs with a low incidence of BP effects, it may be necessary to use Phase III, Phase IV, or even post-approval registry-type data to get an accurate estimate of incidence.

3. What is the effect size and range of BP effects? This information is important for determining CV risk. Defining outliers at the high end of the range of BP changes obviously will be important for making estimates of potential event rates.

4. Is the BP effect dose dependent? Specifically, is there a dose at, and below which, the effect is not seen? Is there a dose where the incidence of this effect is unacceptably high?

5. Do the drug's pharmacokinetic (PK) properties have a relationship to the BP effect? Is the timing of the change in BP or its amplitude predictable by knowing the drug's maximal concentration or other PK properties?

6. Does the BP effect occur in relationship to the time of day of dosing? Is there a predictable time of day when the effect is seen? Could this be ameliorated by changing the time of day of dosing? Or is it an all-day effect seemingly unrelated to when the dosing is given?

7. When does the BP effect occur in terms of the duration of the therapeutic regimen? BP changes may be immediate, or could occur after minutes, hours, days, weeks, or even months of treatment. Conversely, it might appear only after more prolonged chronic therapy. For example, an effect that depends on vascular remodeling might not even be observed during Phase III studies and might only be detected during long-term safety observations.

8. Does the drug convert those with normal BPs into hypertensives or is the BP-raising effect seen mainly in those known to be hypertensive? This is a key question when a drug is being developed for chronic usage. The question assumes that patients with the circulatory changes that underlie hypertension might have a vasculature that is excessively responsive to potential BP-raising stimuli.

9. Could the drug's BP-raising effect be due to interactions with antihypertensive drugs? For instance, it is believed that NSAIDs may have larger-than-average effects on BP in hypertensive patients receiving angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

10. Are there patient characteristics that are predictive of a BP effect? Are such characteristics as age, sex, ethnicity, or concomitant conditions (e.g., pre-existing coronary or other CV disease, diabetes, chronic kidney disease, arthritis) associated with increased probabilities of BP effects?

11. What are the likely mechanisms of a BP effect? This question is analogous to establishing a "proof of concept." Some potential mechanisms could include stimulation of the sympathetic nervous system, endothelin, or the renin angiotensin system. BP could also be increased through other mechanisms, including renal salt retention or long-term vascular remodeling. This information may be critical in strategies for dealing with BP effects.

12. Are other CV risk factors affected? Beyond BP, does the drug cause changes in such factors as heart rate, lipid levels, renal function, or glucose and insulin metabolism?

13. Are the BP raising effects reversible upon drug discontinuation? This is critical information because during treatment regimens intended to last only days or a few weeks it may be acceptable to accept a small increase in BP knowing that this effect will probably disappear when the drug is discontinued.

14. Is it possible to test and recommend a simple treatment strategy for drug-induced BP increases? When there is no practical alternative therapy to a drug that provides a valuable benefit but also raises BP, then it becomes appropriate to evaluate antihypertensive treatment (e.g., calcium channel blockers) that can restore the baseline BP and allow use of the essential drug to continue.

Proposed BP assessments during early human testing

Phase I

This approach incorporates testing to detect the presence of important BP effects in Phase I single-ascending dose (SAD) and multiple-ascending dose (MAD) trials. This allows exploration of BP effect during administration of a wide range of doses accompanied by detailed PK assessment. This will define the pharmacodynamic (PD) properties with respect to BP of the compound during single and multiple doses. As the highest dose exposures typically occur during these trials, concentration relationships to BP changes can be established. Proposed BP measurement uses digital, oscillometric equipment, subjects at rest and in the sitting position during the stay in the clinical research unit. Testing is performed at each dose level, or for first-in-man studies, begun after a reasonable dose level is reached. In MAD studies, data is collected on the first and final days of dosing.

Testing occurs at baseline and approximately 10 postdose

observation timepoints bracketing the presumptive time of maximum concentration (Tmax) until after the presumptive primary elimination half-life (T1/2). Using an example of a drug with a Tmax of 3 hours and T1/2 of 6 hours, BP determinations would be scheduled at 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours in relation to dose. There are duplicate BP determinations at each observation with a third reading if the difference between the first 2 readings is >10mmHg systolic or >5 mmHg diastolic. Ideally, baseline values would be collected at multiple times prior to dosing. After calculation of mean change from baseline for pulse, systolic, diastolic, and mean arterial pressure (MAP) by timepoint at each dose level, analysis of the findings includes comparison to placebo for each of these parameters, and the relationship, for all timepoints and all dose levels combined, of the placebo-adjusted change of the parameters to drug concentration. In addition, there is a tabulation of individual outlier values falling into ranges designated a priori.

Phase II

Collection of detailed BP data during Phase II studies permits the examination of effects that are slow to emerge or which depend on the presence of the underlying disease process, co-morbidities, or concomitant medications. These results are more likely to detect mean effects statistically different from placebo or controls. Also, there are more opportunities for detection of outlier responses and the findings are apt to be more relevant to the clinical setting of use of the drug under development. This proposal includes, in addition to office BP determinations, performance of 24-hour ambulatory blood pressure monitoring (ABPM), which provides unique capability to detect changes—even those of smaller amplitude than those detectable by conventional BP measurements—due to a far larger number of observations and, importantly, during sleep.

During clinic visits, BP assessments occur, envisioning a typical study, on Day 1, Day 7, and Day 28, using digital, oscillometric equipment with subjects in the sitting position and at rest. As in the Phase II proposal, observation times bracket Tmax and continue until about twice Tmax but can be limited to about five timepoints. There is measurement of baseline BP values in triplicate predose at the first visit, with duplicate BPs at each observation and a third reading if necessary, as previously described.

Collect 24-hour ABPM baseline data on the day of the last screening visit, and perform 24-hour ABPM after steady state kinetics are reached, for example on Day 28. Begin the ABPM during the clinical visit and after 24 hours, have the device removed by the patient and returned by courier. Program the ABPM to record values three times per hour for 16 hours (5 a.m. to 10 p.m.) and twice hourly for 8 hours (overnight).

The analysis of the office BP data is identical to that described for Phase I. For ABPM, perform calculation of the hourly mean for pulse, systolic, diastolic, and MAP. In addition to hourly analysis, comparison of day vs. night values gives additional important information as does characterization of results by the following categories: dippers (BP falls at night), non-dippers (no fall), reverse dippers, or extreme dippers.

Discussion

The proposals specify that all data are digital, reproducible, objective, and standardized across subjects, dose groups, visits, and sites. While collecting and analyzing these data impose demands beyond the current design of these trials, these demands are not overly burdensome on investigators, subjects, or statisticians and the information able to be obtained is of high value and, more importantly, is available early in human testing.

There is little experience with the proposed approaches and significant questions remain unanswered. Primarily, without knowing the expected variation within and across subjects in these settings, it is unclear what BP-effect size could be reasonably expected to be determined for each of the studies. As experience grows, it may be possible to define a BP change signal below which most new drugs could be considered to have a minimal risk for hypertensive side-effects. The level for such a cutoff would be modified based on the drug's intended duration of use, the target population, and anticipated concomitant therapies.

While the numbers of subjects exposed is small and it is unlikely that mean changes from baseline will be statistically significant, trends are important and can be identified early in human testing and, in turn, to direct further investigation prior to performing larger studies. In keeping with the general approach presented in the previously cited report of the CSRC (Sager et al.), negative results for BP elevation in early trials would allow more informed planning for BP safety monitoring in later trials. With a positive signal, more intensive monitoring would be necessary, including definition of some or all of the elements referenced in questions 8-12 of the checklist previously summarized.

References

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