

Incorporating Non-Invasive Central Aortic Pressure Monitoring into Drug and Medical Device Development Clinical Trials for Cardiovascular Disease

Background

Incorporation of central aortic blood pressure (cBP) into the development program provides opportunities to improve key decisions along the development pathway for cardiovascular products (drug and medical device), particularly those targeting hypertension.

The SphygmoCor® XCEL system is a dual arterial pressure monitoring medical device consisting of brachial blood (peripheral) pressure (pBP) and central aortic blood pressures (cBP, using partial cuff inflation to record the outgoing brachial waveform), which can be obtained in the clinic in the same patient session with as little as 10 additional seconds to a typical pBP assessment. The SphygmoCor XCEL is the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults.

Central Aortic BP Monitoring be Part of Cardiovascular Product Development Clinical Trials

The advantages of incorporating cBP into clinical development programs (i.e., clinical trials) can be summarized as follows:

1. Confirmation of hypertension at baseline

- Inaccurate baseline values can potentially invalidate all post-intervention results within a subject; therefore, confirmation of hypertension and the absolute BP values is essential. Examples include the following:

Scenario A: Concurrent elevation in brachial and central pressures – confirmed hypertension.

Scenario B: Minimal elevation in pBP that minimally satisfies inclusion criteria. Elevation of cBP confirms acceptability. Low cBP suggests the subject may not be an optimal candidate and can be an exclusion criterion. Prespecified analysis stratifying subjects may be prudent.

Scenario C: Substantial divergence between brachial and central pressures. May suggest potential differential effect of intervention, which can be evaluated (pre-specified analysis).

2. Confirmation of blood pressure values at follow-up. Examples are as follows:

Scenario A: Large differences in absolute values. May indicate white coat hypertension.

Scenario B: Discordant changes from baseline in cBP and pBP values when measurement procedures are correct (e.g., no change in pBP but decline in cBP). The implication is that the therapeutic intervention may be having a differential effect, which has been documented in the past in other trials comparing drugs in different classes. Without cBP, a false interpretation (e.g., no efficacy) could be concluded, when a true drug effect exists.

3. Endpoints for evaluation of therapeutic effect

- Central pressures provide additional and potentially independent information regarding risk of end-organ damage (or probability of reduced risk) and clinical outcomes. This information can be utilized in clinical trials. An example is as follows:

Scenario: Drug in phase II shows minimal change in pBP that does not provide adequate information for assessment of go/no go decision. A clear effect (or absence of effect) on central pressures allows for a more informed decision as to whether to proceed with additional phase II studies or to proceed to phase III.

4. Informing dose selection during phase II dose ranging trials

- A critical decision in drug development is dose selection. Often 3 to 5 doses are evaluated in phase 2 in order to proceed with 1 to 2 doses in phase 3. The decision may also involve dose frequency (e.g., daily or bid). The additional information from central aortic pressures permits more informed decision regarding (a) confirmation of therapeutic effect when the effect and effect size is unclear or variable, (b) magnitude of therapeutic effect, (c) different therapeutic effect than anticipated, (d) signals as to expected adverse effects related to hypotension, and (e) duration of effect. All of the above must be factored into the decisions that can be categorized as either stopping development, implementing additional phase 2, or proceeding to phase 3.

5. Avoiding misleading information due to white coat hypertension.

- White coat hypertension is extremely common. cBP can provide informative information. The scenario where this becomes a consideration is when pBP is elevated and cBP is normal or low. Examples include the following:

Scenario A: pBP is elevated and cBP is normal or low at baseline.

Scenario B: pBP is significantly higher than baseline at follow-up visit, while cBP is the same as baseline visit.

6. Information for final safety evaluation

- Overtreatment (i.e., development of hypotension) is always a concern with the outcomes ranging from (a) mild symptoms to (b) syncopal episodes with falls to (c) end-organ damage (e.g., stroke, syncope, myocardial ischemia). Episodic and infrequent hypotension may only occur in a small subset that are predisposed (e.g., elderly, unrecognized autonomic dysfunction, left and right ventricular failure) and could lead to either failure to achieve regulatory approval or have prominent labeling (warnings,

precautions, contraindications). cBP data can provide early signals and evidence that may determine that a higher dose should either be considered or not be brought forward into phase 3. An example of what could occur is as follows:

Scenario: Large declines in cBP indicative of risk for adverse events in the setting where the pBP declines are considered acceptable and within the target product profile range.

7. Regulatory approval and post-approval communication.

- The incorporation of novel endpoints from cBP that are clinically and physiologically related to the primary outcome of a development program (e.g., hypertension, heart failure), especially for phase 3 clinical trials, provide opportunities for regulatory agency discussions (e.g., supportive data and intended utility of the cBP variables), competitive advantages, and post-approval communications. When such variables are prespecified in a successful development program leading to regulatory approval, appropriate external communication of cBP results can be disseminated and be within regulatory guidance and expectations.

Conclusion

For products targeting cardiovascular disease, incorporation of central aortic blood pressure measurement and monitoring into clinical trials can improve key decisions during development (go/no go, endpoints, population characteristics, benefit-risk profile, dosing, etc.) and enhance the likelihood of both regulatory and commercial success. Based on current technology, the availability of a non-invasive dual arterial pressure measurement system, the compelling clinical rationale and the extensive clinical published research, incorporation of central aortic pressure monitoring into clinical trials, which is complementary to continued reliance on brachial pressure monitoring should be part of drug and medical device development programs for hypertension and other cardiovascular disorders.

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