Appendix 4: Bayesian power prior methodology for HTN-OFF and HTN-ON

The primary effectiveness endpoint of the study is the mean difference in the baseline-adjusted 24-hour ambulatory systolic blood pressure (ASBP) from baseline (screening visit 2) to 3-months post-procedure for the HTN-OFF study. The primary endpoint for the HTN-ON study is based on the mean difference in ASBP from baseline to 6-month post-procedure. The statistical approach for analyzing the primary effectiveness endpoint for the HTN-ON and HTN-OFF is the same. The blood pressure (BP) is applied to ASBP, Office SBP, and other type of blood pressures.

Let $\mu = \mu_t - \mu_c$ represents the treatment effect of BP change comparing treatment (rfRDN) and control (sham) groups where μ_t and μ_c are the BP changes in the treatment and control groups, respectively. Let $\boldsymbol{y} = \{\boldsymbol{y_t}, \boldsymbol{y_c}\}$ and $\boldsymbol{y_0} = \{\boldsymbol{y_{0t}}, \boldsymbol{y_{0c}}\}$ represent the pivotal outcomes and prior outcomes, respectively, where t = treatment and c = control group. Let the hypotheses for the study be the following:

$$H_0: \mu \geq 0$$
$$H_a: \mu < 0$$

The H_0 is rejected if:

$$P\left(\mu < 0 \middle| \boldsymbol{y}, \boldsymbol{y_0}, \hat{\alpha}_0(\boldsymbol{y}, \boldsymbol{y_0}, \lambda, k)\right) > 0.975$$

where $\hat{\alpha}_0(\boldsymbol{y}, \boldsymbol{y_0}, \lambda, k)$ (or $\hat{\alpha}_0$ in short) is the discount parameter which depends on the pivotal outcomes, prior outcomes, and the Weibull shape λ and scale k parameters for the discount function (defined later). In conjunction with a pre-specified decision rule controlling the prior outcomes weight, the estimate of $\hat{\alpha}_0$ represents a measure of similarity between the pivotal and prior outcomes.

The power prior discount function approach is used to estimate μ with estimated $\hat{\alpha}_0$ to discount the strength of the prior outcomes. Note that $\hat{\alpha}_0$ ranges from 0 to 1, where 1 means that 100% of the prior outcomes is used and 0 means that no prior outcomes is used. Before beginning the study, α_{max} value is specified for the maximum strength the prior outcomes can receive. The sponsor assumed $\alpha_{max} = 1$ and mentioned that "*We intend to use the same enrollment criteria for the prior and pivotal studies, and therefore believe that a value of* α_{max} *is appropriate.*" At each interim look and at the final analysis, the sponsor proposed to analyze the outcomes using the power prior discount function method, they indicated that "*this method will discount* α_{max} *to an appropriate value* $\hat{\alpha}_0$ *where* $\hat{\alpha}_0 \leq \alpha_{max}$". The level of discounting is based on the discount function (defined later).

There are four steps in this approach: compare, discount, combine and estimate. In the first step (or the "compare" step), the outcomes from two different sources (prior and pivotal) are compared as described below. In the "discount" step, the discount parameter $\hat{\alpha}_0$ is determined. Using the power prior method and $\hat{\alpha}_0$, the sponsor implements their Bayesian model to combine prior and pivotal ("combine" step) and to compute the posterior probability ("estimate" step).

In the first step (or the "compare" step), for each treatment group, the sponsor planned to fit the model to the prior and pivotal outcomes:

$$y_i = \tilde{\beta}_0 + \tilde{\beta}_1 I(i \in prior) + \tilde{\beta}_2 x_i + \varepsilon_i,$$
$$\varepsilon_i \sim N(0, \tau^2),$$

where $I(i \in prior) = 1$ if the subject is from the prior dataset, and 0 otherwise, y_i is the BP change for the ith observation, and x_i is the mean centered baseline BP for the ith observation. With flat priors on each parameter, the sponsor planned to estimate p^*, the probability that $\tilde{\beta}_1 > 0$, via Monte Carlo sampling. For example, p_t^* is estimated by $P[\tilde{\beta}_1 > 0 | \boldsymbol{y_t}, \boldsymbol{y_{0t}}]$ for the subjects in the treatment group, and p_c^* is estimated by $P[\tilde{\beta}_1 > 0 | \boldsymbol{y_c}, \boldsymbol{y_{0c}}]$ for the subjects in the control group. Having calculated this separately for both the treatment and control groups, they are transformed to p_t and p_c using

$$p = \begin{cases} 2p^* & if\ p^* \leq 0.5 \\ 2(1-p^*) & if\ p^* > 0.5 \end{cases}.$$

For each group, under this transformation, if p_t or p_c are close to 0, there is a high probability that the pivotal outcomes and prior outcomes have different outcomes. The discounting would be applied to reduce the influence of the prior outcomes by the group. On the other hand, for each group separately, if p_t or p_c are close to 1, there is a high probability that the pivotal outcomes and prior outcomes come have similar outcomes. The minimal discounting would be applied to the prior outcomes by the group.

In the "discount" step, the discount parameter is determined. The sponsor planned to scale α_{max} based on the value of p_t and p_c from the "**Compare"** step and set $\hat{\alpha}_0 = \alpha_{max} F(p)$ where $F(p)$ is a function between 0 and 1. A two-sided Weibull function was utilized as follows:

$$F(p) = 1 - e^{-\left(\frac{p}{\lambda}\right)^k},$$

the sponsor planned to use a shape parameter of $k = 3$ and a scale parameter of $\lambda = 0.5$.

Using the power prior method and the discounting parameter $\hat{\alpha}_0$, the sponsor planned to combine the prior and pivotal outcomes together using Bayesian techniques to construct the posterior distribution. The posterior distribution from the combined prior and pivotal outcomes is used to estimate the posterior probability:

$$P\left(\mu < 0 \middle| \boldsymbol{y}, \boldsymbol{y_0}, \hat{\alpha}_0(\boldsymbol{y}, \boldsymbol{y_0}, \lambda, k)\right).$$

Böhm, et al. (Clin Res Cardiol. 2020) provide a detailed discussion of the Bayesian approach used in the HTN-OFF and HTN-ON studies. Note that the posterior distribution is also based on the baseline BP adjusted linear regression model (ANCOVA) to determine the probability of success and the treatment difference between rfRDN and Sham groups.

The sponsor also indicated that "*Under the adaptive procedure, if the pivotal data diverges from the prior data at an interim look, the discount function will discount the strength of the prior data, thus requiring continued enrollment to maintain power to achieve the endpoint. Alternatively, if the prior and pivotal data agree, there will be a smaller penalty from the discount function, thus fewer prospective patients would be needed to maintain power, and enrollment may stop early.*"

As the dynamic borrowing method is novel, FDA also asked for sensitivity analyses to be performed using the more common frequentist approach (using all subjects) for each cohort to provide perspective.

References

Böhm M, Townsend RR, Kario K, Kandzari D, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Hickey GL, Fahy M, DeBruin V, Brar S, Pocock S. Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal) and presence (SPYRAL HTN-ON MED Expansion) of antihypertensive medications: a novel approach using Bayesian design. Clin Res Cardiol. 2020 Mar;109(3):289-302. doi: 10.1007/s00392-020-01595-z. Epub 2020 Feb 7. Erratum in: Clin Res Cardiol. 2020 May;109(5):653. PMID: 32034481; PMCID: PMC7042193.