**SUPPLEMENTAL MATERIAL**

**Clinical Outcomes Stratified by Baseline Functional Class After Initial Combination Therapy for Pulmonary Arterial Hypertension**

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\*No subjects randomized

All centers participated in the study under the US IND.

**Drug Titration**

Tadalafil was initiated at 20 mg and ambrisentan at 5 mg (whether monotherapy or combination therapy), and drugs were blindly uptitrated at week 4 (tadalafil to 40 mg) and week 8 (ambrisentan to 10 mg).

**Statistical Methods**

We analyzed walk distance using the stratified Wilcoxon rank sum test; missing values were imputed using last observation carried forward unless participants had a death or adjudicated hospitalization for worsening PAH in which case worst rank was imputed. The percentage of patients with a satisfactory clinical response was analyzed as a binary endpoint using logistic regression with no imputation for missing values. Post-hoc analyses of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are presented as the geometric mean and geometric mean ratio and analyzed using mixed models repeated measures with no imputation for missing data.

To address the possibility that the 11 class II participants assigned to monotherapy and ultimately hospitalized were substantially different than the overall group of class II participants, we rank-ordered the 155 Class II participants for both NT-pro-BNP and 6MW. We used descending order for NT-proBNP (low rank means a high value of NT-proBNP); similarly, a low rank for 6MWD means a low value for 6MWD. We assigned ties an average rank. For example, the first tie for 6MWD were the two values between Rank 47 and Rank 50 (i.e., ranks 48 and 49), so we assigned the 2 participants ranks of 48.5. The average (overall) rank was an unweighted average of the two separate ranks.

**Baseline characteristics of eleven Class II participants assigned to monotherapy with a subsequent PAH-related hospitalization**

These participants had baseline characteristics similar to the overall class II group in terms of age, sex, geography, and disease etiology. The average NT-pro-BNP for this group was higher than the overall group and the 6MWD was lower (Supplementary Table 1). To gain further insight into the degree of baseline risk, we ranked the 155 participants separately by NT-pro-BNP (in descending order) and 6MW distance so that the lowest numbers reflected the worst state (highest NT-pro-BNP = lowest rank, lowest walk = lowest rank.) The raw data and ranks of these eleven participants with class II symptoms are shown in Supplementary Table 2. The table illustrates that these 11 subjects have ranks ranging from 1 to 143 (out of 155) for 6MWD and 14 to 117 (out of 144 due to missing values) for NT-proBNP. The average ranks for the 11 participants range from 17 to 106. These 11 participants did have 2 of the worst walks (the worst walk and the 5th worst walk), but there were also relatively higher walks in this group. We conclude that the overall mix was similar to the entire group of Class II participants including all of those assigned to combination therapy (who never had a hospitalization).

**Supplementary Table 1: Baseline Characteristics for the Eleven Class II Participants with a PAH-related Hospitalization**

|  |  |
| --- | --- |
|   | Class II participants assigned to monotherapy with a PAH-related hospitalization, n = 11; mean ± SD |
| Age, years  | 52 ± 14 |
| Female | 8 (73%)  |
| North America | 5 (46%) |
| Type of PAH |  |
| Idiopathic/ Heritable PAH | 7 (64%) |
| PAH associated with connective tissue disease | 4 (36%) |
| Baseline walk\*, m  | 360 ± 120 |
| Baseline NT-proBNP\*, ng/L | 1200 ± 890 |

\*Values rounded to two significant digits for ease of comparison

**Supplementary Table 2: Ranking of Eleven Class II Participants with a PAH-related Hospitalization (baseline values)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Participant ID | 6MWD, m | 6MWD Rank | NT-pro-BNP, ng/ml | Pro-BNP Rank | **Overall Rank** |
| 281 | 185.9 | 5 | 1611 | 29 | **17** |
| 1302 | 339.5 | 28 | 2614 | 14 | **21** |
| 287 | 130.1 | 1 | 1268 | 42 | **21.5** |
| 203 | 341.7 | 29 | 1387 | 34 | **31.5** |
| 1295 | 396.5 | 70 | 1839 | 22 | **46** |
| 164 | 449 | 116 | 2554 | 15 | **65.5** |
| 130 | 357.2 | 42 | 159 | 117 | **79.5** |
| 894 | 430.5 | 95.5 | 288 | 95 | **95.25** |
| 1086 | 480.5 | 141 | 747 | 61 | **101** |
| 1005 | 424 | 89.5 | 170 | 115 | **102.25** |
| 1035 | 484.5 | 143 | 607 | 69 | **106** |