may be necessary to unequivocally determine individual benefit of lumacaftor–ivacaftor on clinical outcomes (1, 2).

In summary, our data suggest that FIS of intestinal organoids and *in vivo* biomarkers of CFTR function are sensitive tools for detection and quantification of restoration of CFTR function in response to CFTR-directed therapeutics. However, we did not observe a correlation at the low levels of functional rescue of lumacaftor–ivacaftor in F508del-homozygous patients. We conclude that future studies in a larger group of patients with a spectrum of responsive *CFTR* mutations and more effective CFTR modulators (1, 2, 11) will be required to determine the exact role of patient-derived organoids and *in vivo* biomarkers of CFTR function in predicting clinical efficacy of different CFTR modulators in individual patients to enhance precision medicine for CF. ∎

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The Arousal Threshold as a Drug Target to Improve Continuous Positive Airway Pressure Adherence: Secondary Analysis of a Randomized Trial

To the Editor:

Obstructive sleep apnea (OSA) is common and associated with many adverse health outcomes (1–3). Continuous positive airway

pressure (CPAP) virtually eliminates OSA, but adherence is variable (4). Thus, there has been great interest in interventions to improve CPAP usage, but success has been limited (4). Two recent studies suggest that the nonanatomic trait "low arousal threshold" (ArTH; waking up easily) predicts low CPAP adherence (5, 6). Importantly, the ArTH can be increased with sedatives such as eszopiclone (7) and thus may be a therapeutic target to increase CPAP usage. However, the two prior reports focused on distinct subsets of patients with OSA (post-stroke patients [6]), lacked in part objective adherence data (5), and did not assess the effect of interventions targeting the ArTH on CPAP usage (5, 6). To address these issues, we performed a secondary analysis of a randomized trial that showed that 2 weeks of eszopiclone 3 mg versus placebo at CPAP initiation improved objectively measured CPAP adherence over 6 months in a cohort of patients with general OSA (8). Thus, for the present study, we tested our hypotheses that 1) a low ArTH at baseline predicts low CPAP usage, and 2) the effect of eszopiclone on CPAP adherence is modified by the ArTH. Some of the results of the present study have been previously reported in the form of an abstract (9).

We obtained a deidentified subset of the original data set containing basic demographics, the Epworth sleepiness scores (ESS), OSA parameters, and CPAP adherence at 1 month for 162 subjects (2 subjects in the placebo group piloted study procedures before randomization of 160 subjects; we were unable to identify and remove these 2 nonrandomized subjects). Using a validated formula (10, 11), we estimated the ArTH for each subject based on age, sex, body mass index (BMI), apnea–hypopnea index (AHI, hypopneas defined by 3% desaturations or cortical arousals), oxygen saturation as measured by pulse oximetry (Sp_{O_2}) nadir, and fraction of hypopneas and then dichotomized the ArTH into low versus high using a standard cutoff of 15 cm H_2O (10). The BMI had originally been collected for each subject, but these data could not be retrieved for this secondary analysis. To allow calculation of the ArTH, we imputed individuals' BMI using the mean BMI previously reported for the eszopiclone versus placebo group (mean, 30.3 vs. 30.4 kg/m^2). Missing data for age (number

missing = 3) and Sp_{O_2} nadir (number missing = 6) were minimal and thus not imputed. Outcomes were mean CPAP use per night (primary) and percentage of nights with >4 hours at 1 month (secondary). Using the Wilcoxon rank-sum test, we compared CPAP adherence in subjects 1) with a low versus high ArTH and 2) who received eszopiclone versus placebo stratified by the ArTH. To adjust for potential confounding by baseline characteristics (baseline AHI, ESS, CPAP level, sex, age, and residual AHI), we used median regression (backward selection based on Bayes' information criterion) (6). We used median regression to assess for an interaction between ArTH and study drug (results from a two-way ANOVA were similar but the normality and homogeneous variance assumptions were violated despite log transformation). For the primary analysis, we assumed that subjects who discontinued CPAP within the first month had zero usage per night. In sensitivity analysis, we excluded such patients.

We included 153 of 162 subjects in whom we could estimate the ArTH (9 had missing data for age and/or Sp_{O_2} nadir). Subjects were mostly middle-aged (median, 44 yr [interquartile range (IQR), 36–50]) men (76%) with moderate OSA (AHI, 23/h [IQR, 13–43.5]) and a low ArTH (66%). The low-ArTH subgroup had less severe OSA than the high-ArTH subgroup (mean [SD] AHI, 18.3 [9.8] vs. 58.8/h [27.2]; $P < 0.001$); otherwise, groups were clinically similar: age (43.1 [9.6] vs. 44.6 [9.0] yr; $P = 0.33$), male sex (67.3% vs. 80.2%; $P = 0.11$), assignment to eszopiclone (50.5% vs. 50%; $P = 0.95$), subjective sleepiness (ESS, 12.0 [4.5] vs. 13.5 [4.3]; $P = 0.048$), residual AHI during titration (median 2.7/h [IQR, 0.9–6] vs. 3.4/h [2–11.6]; $P = 0.04$), and prescribed CPAP level (9.4 [2.1] vs. 10.6 [2.6] cm H_2O; $P = 0.003$).

Patients with a low ArTH were more likely to discontinue CPAP during the first month than those with a high ArTH (36.6% vs. 17.3%; $P = 0.02$ using Fisher's exact test). Eszopiclone did not significantly affect the percentage of patients who discontinued CPAP overall or within the ArTH subgroups ($P \geq 0.14$ using Fisher's exact test).

In patients with a low ArTH, median CPAP usage was 2.5 hours less than those with a high ArTH (1.3 h [IQR, 0–3.9] vs. 3.8 h [0.6–5.6]; $P = 0.001$; Figure 1A). Results were similar when adjusting for baseline characteristics (−2.1 h; adjusted $P = 0.003$; the final model
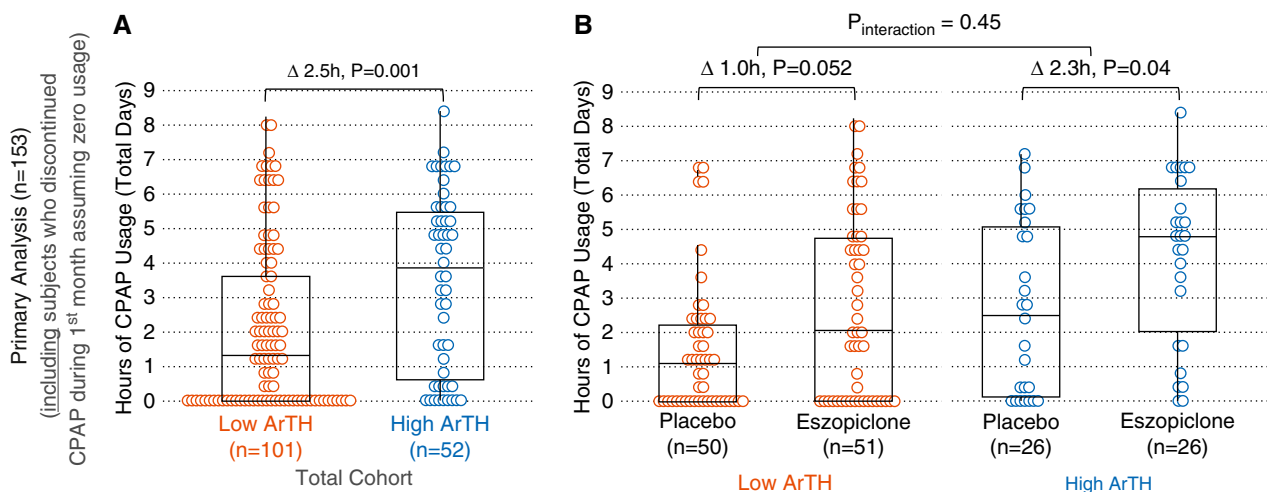

Figure 1. (A) Primary analysis: average hours of nightly continuous positive airway pressure (CPAP) use at 1 month. Boxplots show median (horizontal line), interquartile range (box), and range excluding outliers (vertical bars) for each (sub) group. Deltas (Δ) reflect differences in medians. (B) Subjects with a low arousal threshold (ArTH) who received eszopiclone had a similar CPAP usage as subjects with a high ArTH receiving placebo ($P = 0.82$) but had less CPAP usage than those with a high ArTH who received eszopiclone ($P = 0.01$). Reprinted from Reference 9.

included CPAP level, age, and residual AHI as covariates). Results were also similar in sensitivity analyses adjusting for baseline AHI as a covariate (-2.9 h; adjusted $P = 0.04$), or when excluding the subjects who discontinued CPAP by 1 month (-2.3 h; $P = 0.04$; Figure 2A). Moreover, the difference in median CPAP usage between the low- versus high-ArTH subgroups was numerically similar in women (-2.8 h; $P = 0.09$) and men (-2.3 h; $P = 0.007$), suggesting that sex did not substantially modify this relationship.

Overall, eszopiclone versus placebo increased median CPAP usage by 2.5 h (3.6 h [IQR, 0–5.5] vs. 1.1 h [IQR, 0–2.7]; $P = 0.001$). Among subjects who received eszopiclone, CPAP usage was less in those with a low ArTH than those with a high ArTH (2.1 h vs. 4.8 h; $P = 0.01$; Figure 1B), but usage was similar across ArTH strata when excluding subjects who discontinued CPAP during the first month (4.3 vs. 4.9 h; $P = 0.40$; Figure 2B).

There was no significant interaction between ArTH and study drug in primary ($P = 0.45$; adjusted $P = 0.72$; Figure 1B) or sensitivity ($P = 0.37$; Figure 2B) analyses.

Results were similar for percentage of nights with >4 hours as outcome (data not shown).

We note two major findings: First, in this cohort of patients with general OSA, a low ArTH at baseline was associated with substantially lower CPAP usage at 1 month than a high ArTH at baseline. This finding extends and validates results from two other studies that were performed in specific subsets of patients with OSA and/or used different methods to measure the ArTH and adherence (5, 6). Second, if a low ArTH *causes* low CPAP adherence, then one would expect that eszopiclone, which increases the ArTH, is only/more effective in patients with a low ArTH than those with a high ArTH. In this study, the effect of eszopiclone on CPAP use was not significantly modified by the ArTH, but considering that interaction tests have low power (12), we note the following: among patients who continued using CPAP for 1 month, eszopiclone increased CPAP usage substantially more in subjects with a low ArTH than those with a high ArTH (Figure 2B). Importantly, those with a low ArTH

who received placebo had the lowest usage (2 h), whereas those with a low ArTH who received eszopiclone had a CPAP usage (4.3 h) similar to patients with a high ArTH (3.6 h with placebo; 4.9 h with eszopiclone; $P \geqslant 0.4$). Thus, low-ArTH patients who persist using CPAP may particularly benefit from eszopiclone (which may also improve the AHI off CPAP) (7). However, eszopiclone appeared to improve adherence even in subjects with a high ArTH. The reason for this finding is unclear, but the difference in CPAP usage was largely driven by the higher percentage of patients who discontinued CPAP in the placebo group than in the eszopiclone group (27% vs. 8%; $P = 0.14$; *see* Figure 1B vs. 2B). Because CPAP can lower arousal threshold over time (13), in theory, the medication may be yielding improved adherence by diminishing this impact in patients with OSA with a high baseline arousal threshold. This study had several limitations. First, prior reports suggest that the effect of the ArTH on adherence is modified by the BMI, which could not be explored in our study. Moreover, to estimate the ArTH, we had to impute individual BMIs, which may have resulted in some misclassifications. But we do not think missing data substantially affected our findings because data were likely missing at random, BMI is a minor component of the ArTH formula, and results were similar when using another variant of the formula predicting low versus high ArTH based on three categorical variables (AHI, SpO_2 nadir, and fraction hypopnea; data not shown) (7). Second, other factors may affect CPAP adherence (e.g., comorbidities, nasal congestion, claustrophobia, and psychosocial factors like *a priori* readiness to change behavior or partner support) (14–16), but we were unable to assess this. Third, we were unable to retrieve adherence data beyond 1 month precluding longitudinal analyses to assess the effect of the ArTH on long-term adherence and increase the power of interaction tests. But early adherence is a strong predictor of long-term adherence (17), and results from studies with longer follow-up were similar (5, 6). On the other hand, CPAP tends to lower the ArTH (13), perhaps explaining (in part) the "slowly declining" use seen in some patients (15).
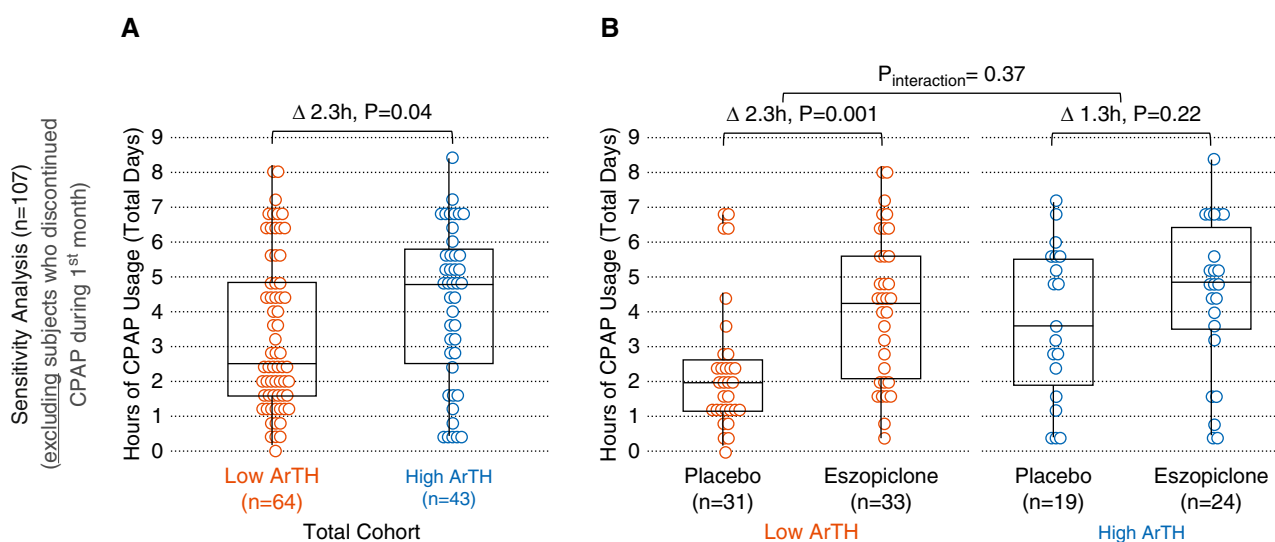

Figure 2. (A) Sensitivity analysis: average hours of nightly continuous positive airway pressure (CPAP) use at 1 month. (B) Subjects with a low arousal threshold (ArTH) who received eszopiclone had a similar CPAP usage as subjects with a high ArTH receiving placebo ($P = 0.51$) or eszopiclone ($P = 0.40$). Reprinted from Reference 9.

In conclusion, we found that a low ArTH is associated with substantially reduced CPAP adherence and that eszopiclone improves CPAP usage overall, especially in subjects with a low ArTH who continued CPAP for 1 month. However, we emphasize that the presented results are based on exploratory *post hoc* analyses. Rigorous interventional trials assessing hard outcomes are needed to better understand the potential risks and benefits of targeting the ArTH to improve CPAP adherence and effectiveness. ∎

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Comparison of Two Approaches to Estimate Driving Pressure during Assisted Ventilation

To the Editor:

Negative pressure swings generated by patients' muscles (Pmus)—which add up to airway pressure generated by the ventilator—are increasingly recognized as a potential source of injury for the lungs, particularly in patients with acute respiratory distress syndrome (1). Precise monitoring of this component requires transduction of esophageal pressure or electrical activity of the diaphragm (2). Recently, however, two surrogated methods, relying on airway pressure waveforms only, have been proposed and validated to estimate the total driving pressure. The first is the static method. Our group reappraised (3) the end inspiratory technique (originally described by Foti and colleagues [4]), which takes advantage of patients' relaxation, normally occurring at the end of inspiration, to