CHEST

# Assessing Daily Life Physical Activity by Actigraphy in Pulmonary Arterial Hypertension

## Insights From the Randomized Controlled Study With Selexipag (TRACE)

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**BACKGROUND:** Reduced daily life physical activity (DLPA) in pulmonary arterial hypertension (PAH) contributes to a poor quality of life.

**RESEARCH QUESTION:** Can actigraphy be used to assess changes in DLPA in patients with PAH receiving selexipag or placebo?

**STUDY DESIGN AND METHODS:** Effect of Selexipag on Daily Life Physical Activity of Patients With Pulmonary Arterial Hypertension (TRACE) was a prospective, multicenter, randomized, placebo-controlled, double-blind, exploratory phase 4 study enrolling patients with PAH in World Health Organization functional class II/III, receiving stable endothelin receptor antagonist with/without phosphodiesterase type 5 inhibitor background therapy. Primary end points were change from baseline to Week 24 in actigraphy-assessed DLPA (recorded by using an accelerometer), including daily time spent in nonsedentary physical activity (NSPA), daily time spent in moderate to vigorous physical activity (MVPA), daily volume of activity, and daily number of steps.

**RESULTS:** At baseline, patients (N = 108) were prevalent, on stable background PAH therapy, and at low risk of disease progression. Patients showed high compliance with wear of the accelerometer throughout the study. From baseline to Week 24, mean daily time spent in NSPA increased by 1.1 min and decreased by 16.7 min in the selexipag and placebo groups (treatment difference [95% CI], 17.8 [−6.0, 41.6] min); mean time spent in MVPA increased by 0.3 min and was reduced by 2.0 min in the selexipag and placebo groups (treatment difference [95% CI], 2.3 [−10.8, 15.4] min); and mean number of daily steps decreased by 0.3 and 201.9 in the selexipag and placebo groups (treatment difference [95% CI], 201.6 [−243.0, 646.2]).

**INTERPRETATION:** TRACE enrolled a prevalent population on background therapy and at low risk of disease progression. Changes in DLPA were small and highly variable, with no statistically significant differences between treatment groups. This patient-centric study was the first randomized trial in PAH to capture high-quality actigraphy data and to describe DLPA in terms of mean/median and variability, which may inform the design of future studies.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov; No.: NCT03078907; URL: www.clinicaltrials.gov

CHEST 2023; 163(2):407-418

**KEY WORDS:** actigraphy; daily life physical activity; pulmonary arterial hypertension; quality of life; selexipag

**ABBREVIATIONS:** 6MWD = 6-min walk distance; DLPA = daily life physical activity; EOT = end of treatment; MVPA = moderate to vigorous physical activity; NSPA = nonsedentary physical activity; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension-Symptoms and Impact questionnaire; RCT = randomized controlled trial; WHO FC = World Health Organization functional class

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## Take-home Points

**Study Question:** Can actigraphy be used to assess changes in DLPA in patients with PAH receiving selexipag or placebo in the exploratory phase 4 TRACE RCT?

**Results:** Patients showed high compliance with wear of the accelerometer throughout the study, and small changes in DLPA parameters were observed in the selexipag and placebo groups.

**Interpretation:** TRACE is the first randomized trial in PAH to successfully collect high-quality actigraphy data. Although changes in DLPA were small and highly variable, high patient compliance supports the potential for monitoring DLPA in future clinical trials.

Pulmonary arterial hypertension (PAH) is a rare and debilitating disease affecting the pulmonary vasculature that can lead to right heart failure.[1] PAH affects all aspects of a patient's life[2] and is characterized by nonspecific symptoms such as reduced exercise capacity and dyspnea.[3] Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure and in daily life can be categorized into occupational, household, conditioning, sports, or other activities.[4] Physical activity is associated with a reduced risk of morbidity/mortality across a range of cardiovascular diseases, and the benefits of physical activity seem greater in those with cardiovascular disease vs those without.[5,6]

Structured tests such as the 6-min walk test typically used to assess the exercise ability of patients with PAH provide a snapshot of physical capacity at the time of the test but do not reflect daily life physical activity (DLPA).[7] The measurement of DLPA allows for continuous evaluation, providing a more comprehensive overview of a patient's physical activity than a single measurement, yet DLPA is not commonly assessed in PAH trials. Reduced DLPA in patients with PAH[7-9] can substantially affect health-related quality of life.[3,7] Patients with PAH were found to have lower scores for both physical and mental components of the 36-Item Short Form Health Survey compared with the general population,[3] and lower DLPA has been associated with greater self-reported mental and physical fatigue.[10] In addition, reduced health-related quality of life as measured by using the 36-Item Short Form Health Survey is negatively associated with survival in patients with PAH.[11] Generally, reduced physical activity leads to increased mortality, which might also affect patients with PAH.[12] A need therefore exists for patient-centric approaches that focus on more tangible benefits, including a general improvement in physical capacity for performing daily tasks.[13]

Actigraphy is a noninvasive method for measuring physical activity.[14] Continuous measurement of DLPA with actigraphy may provide an accurate representation of patients' physical activity and clinical presentation, although this has not been evaluated as a primary end point in PAH clinical trials. It is important to assess DLPA in a randomized controlled trial (RCT) to determine potential changes in physical activity in a controlled setting.

In the event-driven Selexipag (ACT-293987) in Pulmonary Arterial Hypertension (GRIPHON) trial, the oral selective prostacyclin receptor agonist selexipag was shown to reduce the risk of a morbidity/mortality event by 40% compared with placebo in a population of 1,156 patients with PAH.[15] Based on these data, selexipag was approved for the long-term treatment of PAH in adult patients with World Health Organization functional class (WHO FC) II to III.[16] Effect of Selexipag on Daily Life Physical Activity of Patients With Pulmonary Arterial Hypertension (TRACE) aimed to explore whether actigraphy could be used to assess changes in DLPA in patients with PAH receiving selexipag or placebo in an RCT setting.

## Study Design and Methods

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Part of this article has been presented at the virtual CHEST Annual Meeting, October 18-21, 2020, and in abstract form (Howard L, et al. *Chest.* 2020;158:A2449-A2451).

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**DOI:** https://doi.org/10.1016/j.chest.2022.08.2231

### Study Design and Patient Population

TRACE was a prospective, multicenter, randomized, placebo-controlled, double-blind exploratory phase 4 study, initiated on November 8, 2017, and completed on February 20, 2020.[17] The Steering Committee, in collaboration with the sponsor (Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson), designed and oversaw the conduct of the trial and analyzed the data. Ethical approval was received from independent ethics committees/institutional review boards, and the study was conducted in compliance with the Declaration of Helsinki (e-Table 1). Written informed consent was obtained from all enrolled patients. DLPA and quality of life-related data were collected prior to randomization during a baseline period of up to 28 days. Patients were randomized 1:1 to receive selexipag or placebo for 24 weeks (e-Fig 1). Further information on the randomization and blinding processes is provided in e-Appendices 1 and 2. Selexipag titration was performed as previously described.[15] After discontinuation of study treatment, there was a 30-day posttreatment safety follow-up period.

Patients aged 18 to 75 years with PAH (idiopathic, heritable, drug and toxin induced, or associated with connective tissue disease, HIV infection, or corrected congenital heart disease [simple systemic-to-pulmonary shunts ≥ 1 year after repair]) diagnosed by right heart catheterization[18,19] were eligible. Patients were required to have a 6-min walk distance (6MWD) ≥ 100 m and be in WHO FC II to III, without hospitalization or worsening WHO FC in the 30 days prior to screening. Patients had to be receiving an endothelin receptor antagonist alone or in combination with a phosphodiesterase type 5 inhibitor or soluble guanylate cyclase stimulator for ≥ 90 days and at a stable dose for ≥ 30 days prior to randomization. Participation in an exercise-based rehabilitation program was not permitted in the 8 weeks prior to study start or at any point during the study. Full inclusion/exclusion criteria are provided in e-Appendix 3.

### Clinical Assessments

Site visits occurred on Day 1, Week 16, and Week 24, and patients were called from the site weekly during the 12-week titration period, as well as at Weeks 15, 20, and 23 (e-Fig 1). DLPA was recorded with a lightweight (14 g), wrist-worn, validated triaxial accelerometer (GT9X Link, ActiGraph).[20-22] Patients were asked to wear the actigraph on the wrist of their nondominant hand for the duration of the study, 24 h per day and 7 days a week. For analysis of the actigraphy data, a wear-compliant day was defined as a day with at least 7 h of wear-time during wake-time. At least 7 valid days in a 14-day interval were used for the analyses. Wear and wake time were algorithmically defined.[23-25] Raw acceleration data were processed in epochs of 60 s, generating activity counts per minute for each axis and for vector magnitude, and all actigraphy variables were summarized across 14-day windows from baseline (14 days prior to first dose) to Week 24 (days 155-168). Epoch data were uploaded daily via the study-provisioned smartphone, allowing wear time monitoring by the study sites and identification of patients for whom support was required to maintain compliance (e-Fig 2).

Patients were blinded to their activity data and not actively encouraged to increase physical activity. The Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) electronic patient-reported outcome instrument is a PAH-specific questionnaire that assesses symptoms and impacts (e-Appendix 4).[26,27] It was completed at baseline, Week 15, and Week 23, using the study-provisioned smartphone (e-Fig 1). 6MWD, Borg dyspnea score, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were assessed during screening and at Weeks 16 and 24. WHO FC was assessed at all site visits. Safety and tolerability were monitored until 30 days following the end of study treatment.

### Study End Points

TRACE was designed as an exploratory study with a primary focus on DLPA, and therefore all actigraphy variables were considered primary end points. Primary end points were change from baseline to Week 24 in actigraphy-assessed DLPA, which included daily time spent in nonsedentary physical activity (NSPA; minutes and percentage of wake time), and total daily physical activity. DLPA end points were further specified and expanded to include NSPA defined as ≥ 1,853 vector magnitude activity counts per minute (Koster et al[28]) and ≥ 100 y-axis activity counts per minute (Matthews et al[29]), often referred to as one of the Freedson thresholds (Freedson et al[30]), and time spent in moderate to vigorous physical activity (MVPA) defined as ≥ 1,952 y-axis activity counts per minute (Freedson et al[30]). Because Freedson et al[30] measured activity using a monoaxial, hip-worn accelerometer, y-axis counts obtained from the wrist-worn accelerometer used in TRACE were scaled by ActiGraph's scaling algorithm to align with the Freedson methodology. Daily number of steps, as a measurement of total daily activity, was calculated by using ActiGraph's proprietary algorithm for step counting. Additional DLPA primary end points are described in e-Appendix 5. Secondary end points included change from baseline to Week 24 in PAH-SYMPACT scores, 6MWD, Borg dyspnea score, WHO FC, and serum NT-proBNP.

### Statistical Analyses

Because TRACE was designed to be exploratory, there was no formal hypothesis testing or adjustments for multiplicity. The sample size of 100 patients was chosen based on enrollment capabilities. Additional information on sample size calculations is given in e-Appendix 6. Change from baseline to Week 24 and treatment difference (least squares mean) in DLPA, PAH-SYMPACT, 6MWD, and Borg dyspnea score were estimated by using an analysis of covariance model with a covariate for baseline value. Change from baseline (geometric mean ratios) and treatment difference for NT-proBNP were estimated by using an analysis of covariance model with a covariate for baseline value (log scale). WHO FC was analyzed descriptively at baseline and Week 24/end of treatment (EOT), with the shift from baseline presented. Correlation between 6MWD and DLPA parameters (NSPA, MVPA, and number of daily steps) at baseline, Week 16, and Week 24 was analyzed in the overall population using the Pearson correlation coefficient ($r$). Missing data at Week 24 due to premature discontinuations were imputed with the last observation carried forward in the primary and secondary efficacy end points. Invalid actigraphy data at Week 24/EOT were imputed by using a valid last observation carried forward with roll-back (e-Appendix 7). All statistical analyses were conducted by using SAS version 9.4 (SAS Institute, Inc).

## Results

### Patient Characteristics

From November 2017 to June 2019, a total of 119 patients were screened across 29 sites in 10 countries. Of these, 53 patients were randomized to receive selexipag and 55 patients to receive placebo (Fig 1). Overall, baseline characteristics for both groups were generally well balanced, with the exception of a higher proportion of WHO FC III patients and male subjects in the

selexipag group. The population was prevalent (median time from diagnosis [minimum, maximum], 35.8 [4.7, 264.8] months), with 98% (98.1% selexipag, 98.2% placebo) established on double background therapy. Patients displayed a high mean 6MWD of 451 m (453 m selexipag and 450 m placebo) and a low median NT-proBNP level of 166 ng/L (207 ng/L selexipag, 162 ng/L placebo); the majority were in WHO FC II (62.3% selexipag, 74.5% placebo). Overall, 28.3% of the selexipag group and 38.2% of the placebo group had two low-risk criteria and 37.7% and 38.2%, respectively, had three low-risk criteria[31] (Table 1).

In the 14-day interval prior to EOT, the mean ± SD number of wear-compliant days was 13.2 ± 2.9 and 13.0 ± 3.1 in the selexipag and placebo groups, respectively, indicating a high compliance with wear of the accelerometer. At EOT, 93% of patients had at least seven compliant days and 80% had 14 of 14 compliant days. This was reflective of compliance throughout the entirety of the study (e-Table 2).

### Primary End Points

Changes from baseline to Week 24 in actigraphy-assessed DLPA parameters are reported in Table 2. From baseline to Week 24, mean daily time spent in NSPA (based on Koster algorithm) increased by 1.1 min (from 394.1 min at baseline) in the selexipag group and decreased by 16.7 min (from 379.4 min at baseline) in the placebo group (treatment difference [95% CI], 17.8 [−6.0, 41.6] min) (Fig 2, Table 2). The mean time spent in MVPA (based on Freedson algorithm) increased by 0.3 min (from 118.5 min at baseline) in the selexipag group and was reduced by 2.0 min (from 115.0 min at baseline) in the placebo group between baseline and Week 24 (treatment difference [95% CI], 2.3 [−10.8, 15.4] min). The mean ± SD number of daily steps decreased by 0.3 (from 3,729.2 at baseline) and 201.9 (from 3,237.5 at baseline) at Week 24 in the selexipag and placebo groups, respectively (treatment difference [95% CI], 201.6 [−243.0, 646.2]) (Table 2, Fig 2). Small changes from baseline were also observed in the other parameters for both treatment groups, with no significant treatment differences (Table 2). Broad CIs were observed for all DLPA parameters, indicating high variance within and between groups.

### Secondary End Points

Changes from baseline to Week 24 in PAH-SYMPACT domain scores are reported in Table 3. Low scores (< 1) were observed in both the selexipag and placebo groups at baseline. Minor changes from baseline to Week 24, and no differences between the groups, were observed. Changes from baseline to Week 24 in 6MWD, NT-proBNP levels, and WHO FC are shown in Table 4. From baseline to Week 24, mean 6MWD increased by 18.2 m and 9.9 m in the selexipag and placebo groups, respectively (treatment difference [95% CI], 8.4 [−14.2, 31.0] m). The geometric mean (95% CI) for the ratio of baseline to Week 24 NT-proBNP was 0.9 (0.8, 1.1), corresponding to a reduction of 10% for the selexipag group and 1.0 (0.8, 1.1) for the placebo group, with no difference between the groups (treatment difference [95% CI], 0.9 [0.7, 1.2]). From baseline to Week 24, the mean (95% CI) Borg dyspnea score decreased by 0.04

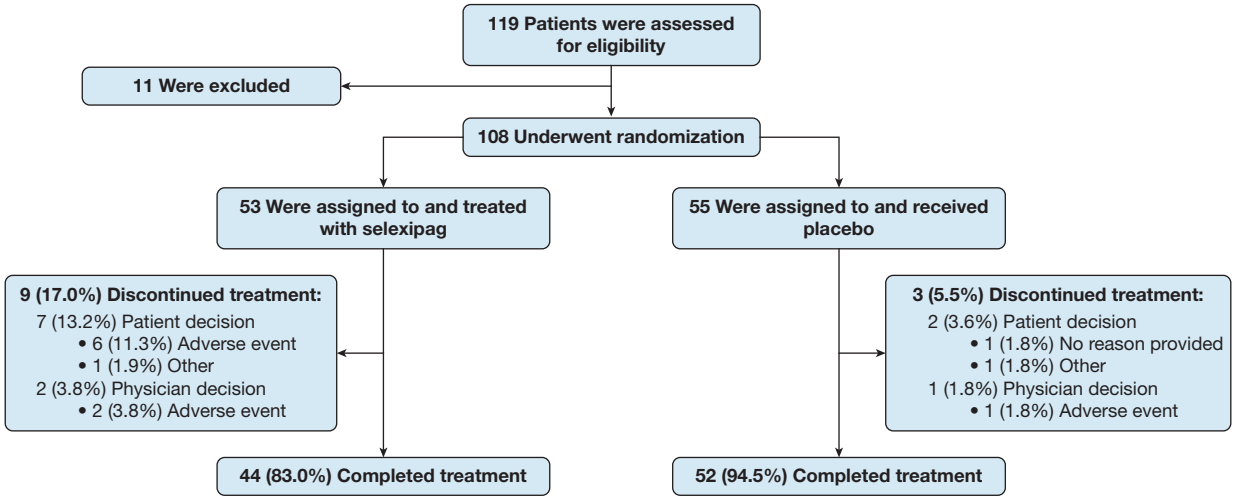


Figure 1 – *Patient disposition. Eleven patients were not randomized to treatment: nine because they did not meet inclusion/exclusion criteria and two because of physician's decision. Five patients in the selexipag group and zero patients in the placebo group discontinued due to prostacyclin-associated adverse events.*

**TABLE 1** ] Demographic and Baseline Characteristics

| Characteristic | Selexipag (n = 53) | Placebo (n = 55) |
|---|---|---|
| Female | 35 (66.0) | 42 (76.4) |
| Age, y | 49.0 ± 14.8 | 49.8 ± 13.6 |
| Age category | | |
| 18-64 y | 42 (79.2) | 43 (78.2) |
| ≥ 65 y | 11 (20.8) | 12 (21.8) |
| Time since diagnosis of PAH at randomization, median (minimum, maximum), mo[a] | 38.1 (5.3, 198.3) | 33.9 (4.7, 264.8) |
| PAH classification | | |
| Idiopathic/heritable | 40 (75.5) | 42 (76.4) |
| Associated with connective tissue disease | 8 (15.1) | 10 (18.2) |
| Associated with congenital heart disease[b] | 4 (7.5) | 1 (1.8) |
| Drug or toxin induced | 1 (1.9) | 1 (1.8) |
| Associated with HIV infection | 0 | 1 (1.8) |
| BMI, kg/m$^2$ | 27.7 ± 4.7 | 27.0 ± 6.1 |
| 6MWD, m | 453.1 ± 129.7 | 449.5 ± 98.9 |
| NT-proBNP, median (minimum, maximum), ng/L | 207.0 (36, 9,811) | 162.0 (16, 3,871) |
| WHO FC | | |
| II | 33 (62.3) | 41 (74.5) |
| III | 20 (37.7) | 14 (25.5) |
| PAH-specific therapy | | |
| ERA only | 1 (1.9) | 1 (1.8) |
| ERA + PDE5i/sGC | 52 (98.1) | 54 (98.2)[c] |
| No. of low-risk criteria[d] | | |
| 0-1 | 18 (34.0) | 13 (23.6) |
| 2 | 15 (28.3) | 21 (38.2) |
| 3 | 20 (37.7) | 21 (38.2) |

Data are No. (%) or mean ± SD, unless otherwise indicated. 6MWD = 6-min walk distance; ERA = endothelin receptor antagonist; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitor; sGC = soluble guanylate cyclase stimulator; WHO FC = World Health Organization functional class.

[a]Calculated by counting the number of days between the (imputed) PAH diagnosis date and the randomization date divided by 30.4.

[b]Simple systemic-to-pulmonary shunts ≥ 1 year following repair.

[c]Protocol deviation: one patient received three therapies at baseline (ERA + PDE5i/sGC + prostacyclin and its analogs), discovered after the patient completed the study.

[d]Defined as WHO FC I/II, 6MWD > 440 m, and NT-proBNP level < 300 ng/L.[31]

(–0.6, 0.5) in the selexipag group and increased by 0.2 (–0.3, 0.7) in the placebo group. There was no significant treatment difference between the groups. At Week 24, WHO FC remained unchanged from baseline for most patients (75.0% selexipag, 80.0% placebo), with improvements seen for 17.3% and 18.2% of selexipag-treated patients and patients receiving placebo, respectively.

To assess whether exercise capacity correlates with DLPA, the correlation between DLPA and 6MWD was analyzed at baseline, Week 16, and Week 24 in the overall population (N = 108). A strong correlation was observed at all time points between 6MWD and daily number of steps ($r$ = 0.55-0.65) compared with a moderate correlation between 6MWD and daily time spent in NSPA (Koster) ($r$ = 0.31-0.38) or MVPA (Freedson) ($r$ = 0.31-0.41) (Table 5).

### *Safety*

The median (minimum, maximum) exposure to study treatment was 24.1 (1.7, 27.7) weeks and 24.3 (9.4, 27.6) weeks in the selexipag and placebo groups, respectively (Table 6). The most common adverse events in the selexipag group were headache, diarrhea, nausea, pain in jaw, and vomiting (Table 6). Eight (15.1%) patients in the selexipag group and one

**TABLE 2** ] Change From Baseline to Week 24 in Actigraphy-Assessed DLPA

| Variable | Selexipag (n = 53) | | Placebo (n = 55) | | Treatment Difference[a] (95% CI) |
|---|---|---|---|---|---|
| | Baseline | Change From Baseline[a,b] (95% CI) | Baseline | Change From Baseline[a,b] (95% CI) | Selexipag – Placebo |
| Daily time, min | | | | | |
| NSPA (Koster) | 394.1 ± 101.1 | 1.1 (−15.9, 18.1) | 379.4 ± 121.8 | −16.7 (−33.4, −0.04) | 17.8 (−6.0, 41.6) |
| NSPA (Freedson) | 666.1 ± 102.3 | −13.3 (−32.6, 6.1) | 651.4 ± 114.5 | −27.1 (−46.1, −8.1) | 13.8 (−13.4, 40.9) |
| MVPA (Freedson) | 118.5 ± 57.6 | 0.3 (−9.1, 9.6) | 115.0 ± 67.2 | −2.0 (−11.2, 7.1) | 2.3 (−10.8, 15.4) |
| Daily time, % | | | | | |
| NSPA (Koster) | 38.2 ± 9.2 | 1.0 (−0.7, 2.7) | 36.5 ± 11.5 | −0.2 (−1.9, 1.4) | 1.3 (−1.1, 3.6) |
| NSPA (Freedson) | 64.4 ± 8.8 | 0.3 (−1.4, 2.0) | 62.7 ± 11.1 | −0.4 (−2.0, 1.3) | 0.7 (−1.7, 3.1) |
| MVPA (Freedson) | 11.5 ± 5.5 | 0.3 (−0.7, 1.2) | 11.0 ± 6.4 | 0.3 (−0.6, 1.2) | −0.1 (−1.4, 1.3) |
| Volume of activity during wake time | | | | | |
| Total daily activity, counts/min | 1,888.3 ± 485.5 | 34.5 (−55.6, 124.5) | 1,823.6 ± 615.6 | 13.8 (−74.6, 102.2) | 20.7 (−105.6, 147.0) |
| NSPA (Koster), counts/min | 1,609.5 ± 497.3 | 40.3 (−52.0, 132.6) | 1,552.0 ± 625.9 | 12.8 (−77.8, 103.4) | 27.5 (−102.0, 157.0) |
| NSPA (Koster), counts | 1,659,780 ± 538,094 | 6,609 (−85,317, 98,535) | 1,618,025 ± 666,402 | −51,800 (−142,038, 38,438) | 58,409 (−70,444, 187,263) |
| Daily No. of steps | 3,729.2 ± 2,327.2 | −0.3 (−316.5, 316.0) | 3,237.5 ± 2,038.4 | −201.9 (−512.3, 108.6) | 201.6 (−243.0, 646.2) |
| Daily No. of steps per min wake time | 3.6 ± 2.3 | 0.1 (−0.3, 0.4) | 3.1 ± 1.9 | −0.02 (−0.3, 2.9) | 0.1 (−0.4, 0.5) |

Data at baseline are expressed as mean ± SD. DLPA = daily life physical activity; MVPA = moderate to vigorous physical activity; NSPA = nonsedentary physical activity.
Koster et al[28]: NSPA defined as ≥ 1,853 vector magnitude activity counts per min; Freedson et al[30]: NSPA defined as ≥ 100 y-axis activity counts per min and MVPA defined as ≥ 1,952 y-axis activity counts per min.
[a]Least squares mean change from baseline and treatment difference were estimated by using an analysis of covariance model with baseline value as covariate.
[b]Week 24 or last postbaseline value.

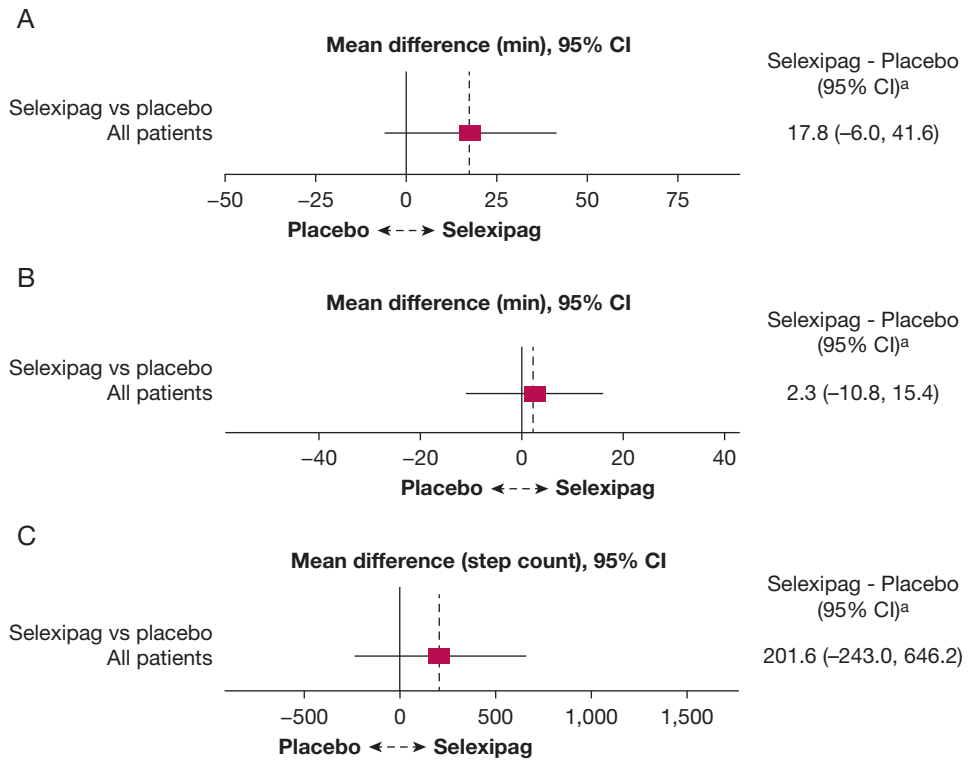


Figure 2 – *Change from baseline to Week 24 in daily time spent in NSPA (A), daily time spent in MVPA (B), and daily number of steps during wake time (C).* [a]*Change from baseline and treatment difference are estimated by analysis of covariance model with baseline value as covariate. MVPA = moderate to vigorous physical activity; NSPA = nonsedentary physical activity.*

(1.8%) in the placebo group discontinued due to an adverse event. No patients died.

## Discussion

The TRACE exploratory study used a patient-centric approach to assess physical activity and PAH symptoms and their impacts on daily life; it was the first exploratory RCT in PAH to use actigraphy-assessed DLPA as a primary end point. In this 24-week exploratory study, small changes in DLPA parameters, PAH-SYMPACT scores, and functional parameters were observed in the selexipag and placebo groups, with no

**TABLE 3** ] Change From Baseline to Week 24 in PAH-SYMPACT Domain Scores

| Domain Score[a] | Selexipag (n = 53) | | Placebo (n = 55) | | Treatment Difference[c] (95% CI) Selexipag – Placebo |
|---|---|---|---|---|---|
| | Baseline | Change From Baseline to Week 24[b,c] (95% CI) | Baseline | Change From Baseline to Week 24[b,c] (95% CI) | |
| Symptoms | n = 44 | | n = 52 | | |
| Cardiopulmonary symptoms | 0.72 ± 0.45 | −0.03 (−0.13, 0.07) | 0.76 ± 0.52 | −0.08 (−0.17, 0.01) | 0.04 (−0.09, 0.18) |
| Cardiovascular symptoms | 0.36 ± 0.40 | 0.00 (−0.09, 0.09) | 0.40 ± 0.48 | −0.04 (−0.12, 0.04) | 0.04 (−0.08, 0.16) |
| Impacts | n = 40 | | n = 50 | | |
| Physical impact | 0.95 ± 0.81 | −0.04 (−0.21, 0.13) | 0.95 ± 0.75 | −0.07 (−0.23, 0.08) | 0.03 (−0.20, 0.26) |
| Cognitive/ emotional impact | 0.71 ± 0.73 | −0.03 (−0.20, 0.14) | 0.88 ± 0.68 | −0.07 (−0.22, 0.08) | 0.04 (−0.19, 0.27) |

Data at baseline are presented as mean ± SD. PAH-SYMPACT = Pulmonary Arterial Hypertension-Symptoms and Impact questionannaire.
[a]PAH-SYMPACT scores were assessed by using a five-point Likert scale, ranging from 0 to 4, with higher scores indicating greater symptom severity or worse impact.
[b]Week 24 or last postbaseline value.
[c]Least squares mean change from baseline and treatment differences were estimated by using an analysis of covariance model with baseline value as covariate.

**TABLE 4** ] Change From Baseline to Week 24 in 6MWD, NT-proBNP, and WHO FC

| Variable | Selexipag (n = 53) | | Placebo (n = 55) | | Treatment Difference (95% CI) Selexipag – Placebo |
|---|---|---|---|---|---|
| | Baseline | Change From Baseline[a] (95% CI) | Baseline | Change From Baseline[a] (95% CI) | |
| 6MWD, m | n = 50 | | n = 54 | | |
| | 448.6 ± 130.3 | 18.2 (2.0, 34.5)[b] | 452.5 ± 97.3 | 9.9 (−5.8, 25.5)[b] | 8.4 (−14.2, 31.0)[b] |
| Borg dyspnea score[c] | 3.9 ± 2.4 | −0.04 (−0.6, 0.5)[b] | 2.8 ± 2.0 | 0.2 (−0.3, 0.7)[b] | −0.2 (−1.0, 0.5)[b] |
| NT-proBNP, ng/L | n = 51 | | n = 53 | | |
| | 800.9 ± 1,698.4 | 0.9 (0.8, 1.1)[d] | 318.8 ± 656.5 | 1.0 (0.8, 1.1)[d] | 0.9 (0.7, 1.2) |
| WHO FC, No. (%) | II: 33 (62.3)<br>III: 20 (37.7) | 4 (7.7) worsened<br>39 (75.0) unchanged<br>9 (17.3) improved[e] | II: 41 (74.5)<br>III: 14 (25.5) | 1 (1.8) worsened<br>44 (80.0) unchanged<br>10 (18.2) improved | NA |

Data at baseline are expressed as mean ± SD unless otherwise stated. Analysis of change from baseline required both baseline and postbaseline values. 6MWD = 6-min walk distance; NA = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; WHO FC = World Health Organization functional class.
[a]Week 24 or last postbaseline value.
[b]Least squares mean change from baseline and treatment difference were estimated by using an analysis of covariance model with baseline value as covariate.
[c]Borg dyspnea score is rated 0 to 10, with 0 indicating no difficulty in breathing and 10 indicating maximal difficulty in breathing.
[d]Geometric least squares mean ratio (95% CI) estimated by using an analysis of covariance model with baseline value (log scale) as covariate.
[e]One patient had missing data.

statistically significant differences between groups. The high level of patient compliance in TRACE shows the feasibility of using wearable technology to continuously monitor patients with PAH over an extended period.

TRACE comprised a prevalent population of PAH patients with 6MWD and NT-proBNP levels indicative of low risk and with the majority in WHO FC II. In this mildly symptomatic population, no or small changes in DLPA, functional parameters, NT-proBNP, and PAH-SYMPACT were observed at Week 24 in the placebo group, indicating no significant disease progression over the 24 weeks of the study. A similar pattern was observed in the selexipag group. The short time period, small changes, and small sample size may have impeded the detection of treatment differences. In the event-driven GRIPHON study, which enrolled a large PAH population (N = 1,156) with more severe disease, selexipag reduced the risk of disease progression by 40%, with a treatment effect on 6MWD of 12 m at week 26. Patients in GRIPHON were also treated for a longer period of time than those in TRACE (median exposure to selexipag, 70.7 weeks vs 24.1 weeks, respectively).[15] Furthermore, in a placebo-controlled phase 2 trial of 43 patients with PAH receiving stable endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor

**TABLE 5** ] Correlation Between Actigraphy-Assessed DLPA End Points and 6MWD at Baseline, Week 16, and Week 24

| Variable | Overall Population (N = 108) | | | | | |
|---|---|---|---|---|---|---|
| | Baseline (N = 108)[a] | | Week 16 (n = 100)[a] | | Week 24 (n = 89)[a] | |
| | *r* | *P* Value | *r* | *P* Value | *r* | *P* Value |
| Daily time, min | | | | | | |
| NSPA (Koster) | 0.31 | .0010 | 0.38 | < .0001 | 0.34 | .0009 |
| MVPA (Freedson) | 0.31 | .0010 | 0.41 | < .0001 | 0.38 | .0002 |
| No. of steps during awake time | 0.55 | < .0001 | 0.65 | < .0001 | 0.58 | < .0001 |

Data are presented as Pearson correlation coefficients (*r*). 6MWD = 6-min walk distance; DLPA = daily life physical activity; MVPA = moderate to vigorous physical activity; NSPA = nonsedentary physical activity. Koster et al[28]: NSPA defined as ≥ 1,853 vector magnitude activity counts per min; Freedson et al[30]: MVPA defined as ≥ 1,952 y-axis activity counts per min.
[a]Number of patients with assessment for both DLPA end point and 6MWD.

**TABLE 6** ] Exposure and Safety

| | Selexipag (n = 53) | Placebo (n = 55) |
|---|---|---|
| Exposure to study treatment, median (minimum, maximum), wk | 24.1 (1.7, 27.7) | 24.3 (9.4, 27.6) |
| AEs, No. (%) | | |
| Patients with ≥ 1 AE | 53 (100.0) | 53 (96.4) |
| Patients with ≥ 1 serious AE | 3 (5.7) | 6 (10.9) |
| Patients with ≥ 1 AE leading to discontinuation of study treatment | 8 (15.1) | 1 (1.8) |
| Patients with most frequent AEs, No. (%)[a] | | |
| Headache | 41 (77.4) | 26 (47.3) |
| Diarrhea | 28 (52.8) | 23 (41.8) |
| Nausea | 22 (41.5) | 15 (27.3) |
| Pain in jaw | 20 (37.7) | 5 (9.1) |
| Vomiting | 13 (24.5) | 4 (7.3) |
| Arthralgia | 11 (20.8) | 8 (14.5) |
| Pain in extremity | 11 (20.8) | 1 (1.8) |
| Dizziness | 7 (13.2) | 7 (12.7) |
| Dyspepsia | 6 (11.3) | 0 |
| Myalgia | 6 (11.3) | 3 (5.5) |
| Upper respiratory tract infection | 6 (11.3) | 6 (10.9) |
| Flushing | 5 (9.4) | 6 (10.9) |
| Nasopharyngitis | 5 (9.4) | 14 (25.5) |
| Back pain | 4 (7.5) | 6 (10.9) |
| Dyspnea | 4 (7.5) | 6 (10.9) |
| Noncardiac chest pain | 2 (3.8) | 7 (12.7) |

AE = adverse event.
[a]Ten percent or more in any group.

therapy, add-on treatment with selexipag improved hemodynamics with a treatment effect on pulmonary vascular resistance of 30.3% at week 17, and an increase in mean 6MWD from baseline by 24.7 m in the selexipag group.[32] Tolerability for selexipag in TRACE was in line with that observed in GRIPHON[15] and the known safety profile of selexipag. No patients died during the study.

Small and variable changes in DLPA were observed in TRACE, and although their clinical relevance has yet to be established, these results can be used to inform the use of actigraphy for the measurement of DLPA in future trial design. There was a marked difference in the daily time spent in NSPA between the thresholds defined by Koster et al[28] and Freedson et al[30] (eg, 6.6 h vs 11.1 h and 6.3 h vs 10.9 h in the selexipag and placebo groups, respectively). Previous studies in PAH have recorded disparate levels of daily active time, ranging from 14.6 h daytime activity[33] to 3.7 h of daily active time (30 min of which was moderate),[12] to 0.7 h of moderate activity with > 22 h of sedentary activity.[34] Given that the type of actigraph used, its positioning, and the definition of activity levels can vary considerably between studies, it is difficult to make direct comparisons to the results reported in TRACE. Calculating NSPA using the threshold defined by Koster et al[28] may be more appropriate, considering that this was developed using the same device and wrist-worn location used in TRACE, whereas the threshold defined by Freedson et al[30] was designed for use with a hip-worn actigraph. One study recorded patients with PAH spending 85% of time in sedentary activity using a hip-worn actigraph while wrist/arm activity was not recorded.[10] It can therefore be expected to observe less sedentary activity time using a wrist-worn device. This highlights the need for standardization across methodologies used in future trials to enable meaningful comparisons between

studies. In line with previous work,[10,35,36] the results of the correlation analysis between 6MWD and DLPA parameters support the use of daily number of steps to monitor exercise capacity in a daily life setting and could be considered as an end point in clinical studies.

Because the variability and minimally important difference of DLPA parameters in PAH have not been established, sample size in TRACE was estimated based on recruitment feasibility. A larger population and longer observation period may be considered for future trials. Clinical studies in PAH show that patients have a less active lifestyle due to the limitations imposed by the disease.[7,8] Patients with PAH who are accustomed to a certain level of limited physical activity may not increase their activity if not encouraged, even if they are able to.[37] The fact that TRACE patients were not encouraged to increase their activity may have contributed to the limited changes to DLPA parameters. Indeed, home-based intervention programs for patients with PAH can result in an increased intensity of DLPA,[38] which should be considered in future trials in which DLPA is measured to evaluate a treatment effect. Common barriers to physical activity reported by patients with PAH include "lack of energy, lack of self-discipline, and lack of interest" in exercise,[39] and interventions to address these barriers could also be considered in future trials.

The high levels of compliance observed in TRACE provide strong evidence that DLPA can be monitored and used successfully in clinical practice and/or in a clinical trial setting. TRACE also highlights the potential for remote data collection in future trials, with the use of actigraphy and electronic patient-reported outcome tools possibly reducing travel to study sites, thereby lessening the burden of study participation. Considering the COVID-19 pandemic, a time when remote data monitoring has become necessary, such tools become yet more important. Monitoring of DLPA in PAH clinical trials can complement the traditional hemodynamic and functional end points and help complete our holistic understanding of patients and their disease, which would benefit both patients and health-care providers.

Given the exploratory nature of the analysis, the results should be interpreted with caution. Furthermore, DLPA end points were quantitative measurements, subjected to the influence of the weather, season, and regional variations in lifestyle habits,[40] which may have masked disease-relevant changes in physical activity and contributed to the high variability in the data. In addition, the study duration of 24 weeks may not have been long enough for the impacts on quality of life and physical activity to become apparent, particularly given that titration of selexipag to a patient's maximal tolerated dose occurs over a 12-week period.

## Interpretation

TRACE was a patient-centric, exploratory and technologically innovative study using actigraphy-assessed DLPA measures as primary end points, and was the first randomized trial in patients with PAH to collect high-quality actigraphy data. This supports the potential for monitoring DLPA in future clinical trials. Further studies are needed to explore the optimal use of actigraphy in PAH, concentrating on aspects such as patient selection, duration of follow-up, choice of end point, and encouragement to increase physical activity.


## Funding/Support

This study was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson.


## Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: L. S. H. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, Gossamer Bio, and Lung Biotechnology; has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson; has received speakers fees from Bayer PLC, Janssen Pharmaceutical Companies of Johnson & Johnson, and Merck; has received support for attending meetings and/or travel from Janssen Pharmaceutical Companies of Johnson & Johnson; has been a member of an advisory board for Acceleron, Janssen Pharmaceutical Companies of Johnson & Johnson, and Merck; and is a shareholder in iOWNA and Circular. S. R. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received research grants from AstraZeneca, Bayer, Janssen Pharmaceutical Companies of Johnson & Johnson, and Novartis; has received consulting fees from and been an advisory board member for Abbott, Acceleron, Bayer, BMS, Gilead, Janssen Pharmaceutical Companies of Johnson & Johnson, MSD, Novartis, Pfizer, United Therapeutics,

and Vifor; has received honoraria from Abbott, Bayer, BMS, Ferrer, Janssen Pharmaceutical Companies of Johnson & Johnson, MSD, Novartis, Pfizer, UT, and Vifor; and has been a past chair for the European Society of Cardiology, member of the Pulmonary Circulation and Right Ventricular Function working group, and is currently a 2022 task force chair. R. P. F. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received grants or contracts from the National Heart, Lung, and Blood Institute; has received consulting fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Liquidia, ShouTi, Altavant, Gossamer Bio, and Bayer; has received honoraria from United Therapeutics, France Foundation, and Janssen Pharmaceutical Companies of Johnson & Johnson; and has participated on a data safety monitoring board/advisory board for Janssen Pharmaceutical Companies of Johnson & Johnson and Liquidia. A. R. H. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received grants from the National Institutes of Health, the Cardiovascular Medical Research and Education Fund, and Imara; has received consultancy fees from Acceleron, Bayer, Gossamer Bio, Janssen Pharmaceutical Companies of Johnson & Johnson, and United Therapeutics; and holds stock/stock options in Tenax Therapeutics. T. P. and S.-F. H. S. are employees of Actelion Pharmaceuticals Ltd. H. S. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received consulting fees from Janssen Pharmaceutical Companies of Johnson & Johnson; and is a stockholder in Bellerophon Therapeutics, Inc. M. H. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, Acceleron, and Merck; has received research funding from Janssen Pharmaceutical Company of Johnson & Johnson; has received grants or contracts from Acceleron, Janssen Pharmaceutical Companies of Johnson & Johnson, and Merck; has received consulting fees from Acceleron, Janssen Pharmaceutical Companies of Johnson & Johnson, and Merck; has received speaker fees from AOP Orphan Pharmaceuticals, Janssen Pharmaceutical Companies of Johnson & Johnson, and Merck; and has participated on an advisory board for Acceleron, Janssen Pharmaceutical Companies of Johnson & Johnson, Merck, and United Therapeutics. I. R. P. has served as a steering committee member for Acceleron, Janssen Pharmaceutical Companies of Johnson & Johnson, and United Therapeutics; has served as an adjudication committee member for Pfizer; has received grants or contracts from Janssen Pharmaceutical Companies of Johnson & Johnson, PhaseBio, Tenax, and United Therapeutics; has received consultancy fees from Altavant; has received payment for lectures from Janssen Pharmaceutical Companies of Johnson & Johnson; and has received payment for expert testimony from Bayer.

## Acknowledgments

**Author contributions:** L. S. H. is the guarantor of the manuscript and takes responsibility for the content of the manuscript, including the data and analysis. L. S. H., S. R., R. P. F., A. R. H., H. S., M. H., and I. R. P. (members of the study steering committee) contributed to the conception and design of the study in collaboration with the funders and were involved in the collection and interpretation of the data. S.-F. H. S. was involved in the statistical analyses. All authors were involved in development of the first draft of the manuscript, with medical writing assistance funded by the sponsor and provided by eluSCIdate Ltd.

**Role of sponsors:** Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, participated in the design of the study, data analysis, interpretation, and preparation of the manuscript.

**Other contributions:** The authors thank Yoko Shiraga, MSc, for her contribution to statistical analyses and comments on the manuscript. Medical writing support was provided by Iain Haslam, PhD, and Laura Corbett, PhD, of eluSCIdate Ltd, Meggen, Switzerland and was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson.

**Additional information:** The e-Appendixes, e-Figures, and e-Tables are available online under "Supplementary Data."

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