BAY 2253651 for the treatment of obstructive sleep apnoea: a multicentre, double-blind, randomised controlled trial (SANDMAN)

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To the Editor:

For obstructive sleep apnoea (OSA), few mechanical treatment options are available and no pharmacotherapy is approved [1–3]. However, safe and efficacious pharmacotherapy would have substantial appeal for many people with OSA.

A promising target is pharmacological treatment increasing upper airway stability by activating the genioglossus muscle. Its activation by the central respiratory control system is importantly modified by mechanoreceptive reflex mechanisms operating locally in the upper airways and modulated by changes in pharyngeal pressure [4–6]. It has been shown that genioglossus muscle activity and reflex modulation to changes in airway pressure are sleep stage dependent [7–9]. Many OSA patients have apnoea-free intervals in which genioglossus muscle activity is only 25–40% higher compared with sleep phases with frequent obstructive apnoeas [10].

Based on an animal model, one promising pharmacological agent which targets genioglossus muscle activation by amplifying upper airway reflex activity is BAY 2253651 [11]. This agent is a potent TASK-1 and TASK-3 potassium channel blocker with a high selectivity. The degree to which BAY 2253651 increases genioglossus muscle activity and thus improves OSA severity in humans is unknown. Accordingly, we performed a first-in-patient randomised, multicentre, double-blind, placebo-controlled, parallel group-comparison study to investigate the efficacy and safety of BAY 2253651 for the treatment of OSA.

Adults currently on treatment for OSA with continuous positive airway pressure (CPAP) (⩾3 months), with an apnoea–hypopnoea index (AHI) of 15–50 h^{-1} after 48 h of CPAP withdrawal documented by polysomnography (PSG; night 1) (table 1) and at least 4 h of sleep time, were eligible to participate in the study. As genioglossus muscle activation alone in very severe and multifactorial OSA (*i.e.* AHI >50 h^{-1}) is less likely to be efficacious, these individuals were not enrolled.

Exclusion criteria included neck circumferences ⩾44 cm, known severe respiratory tract allergies and known allergies or hypersensitivity to the study drugs, severely impaired breathing/nasal congestion within 2 days prior to randomisation, intake of a nasal decongestant during the intervention time, use of any topical medication containing local anaesthetics for nose and throat within 7 days before first investigational medicinal product administration, intake of medication for insomnia within 24 h prior to each PSG, history of severe heart failure or severe COPD, heavy smoking, and regular daily consumption of more than 1 L of xanthine-containing beverages.

All participants provided informed consent and were investigated at tertiary centres by an experienced investigator. The trial was registered *a priori* (ClinicalTrials.gov identifier: NCT03603678; EudraCT-number 2017-001851-29) and an independent data monitoring committee was delegated.

Shareable abstract (@ERSpublications)
BAY 2253651 is a nasally applied genioglossus muscle activator *via* pharyngeal mucosal receptor stimulation (potassium channel blocker) aimed to treat obstructive sleep apnoea. Although well-tolerated and safe, there was no significant therapeutic effect. https://bit.ly/3zDbyia

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TABLE 1 Baseline characteristics and summary statistics for polysomnographic variables for night 1 (off continuous positive airway pressure (CPAP)) and night 2 (intervention) visits (part A)

Parameter	Visit	Placebo	BAY 2253651
Age (years)	Baseline	68.2±6.0	58.6±8.0
Male sex	Baseline	8 (47.1%)	14 (82.4%)
Body mass index (kg·m^{-2})	Baseline	32.39±5.09	33.19±7.03
Neck circumference (cm)	Baseline	39.85±2.83	41.44±2.60
ESS score (points)	Baseline	8.6±3.1	6.2±3.4
AHI (0–4) (h^{-1})	Night 1	27.79±13.65 (2.7 to 50.4)	30.46±14.37 (9.9 to 65.9)
	Night 2	29.83±16.22 (5.9 to 73.6)	32.90±13.67 (15.4 to 67.4)
	Δ night 1 to 2	2.04±14.49 (−17.2 to 37.0)	2.44±19.59 (−32.7 to 50.6)
ODI >4% (h^{-1})	Night 1	28.25±11.58 (5.0 to 48.6)	29.79±9.96 (13.1 to 48.3)
	Night 2	29.69±10.41 (12.8 to 54.5)	31.86±11.44 (7.4 to 47.0)
	Δ night 1 to 2	1.45±8.41 (−6.4 to 26.1)	2.07±8.79 (−10.6 to 19.7)
Sleep efficiency (%)	Night 1	82.30±12.19 (57.3 to 97.7)	85.38±8.49 (63.8 to 98.2)
	Night 2	82.70±10.57 (63.5 to 95.5)	86.36±7.33 (70.2 to 95.2)
	Δ night 1 to 2	0.40±11.17 (−23.3 to 18.3)	0.98±6.64 (−9.3 to 12.3)
Snoring events	Night 1	219.07±68.42 (145.0 to 343.0)	250.00 ±101.71 (16.0 to 405.0)
	Night 2	248.60±118.16 (26.0 to 425.0)	285.81±124.59 (50.0 to 474.0)
	Δ night 1 to 2	29.53±111.80 (−246.0 to 151.0)	35.81±108.46 (−112.0 to 308.0)
Total sleep time (h)	Night 1	5.94±0.87 (4.4 to 7.7)	6.62±0.96 (5.3 to 8.6)
	Night 2	6.27±0.96 (4.0 to 7.6)	7.09±0.78 (5.8 to 9.1)
	Δ night 1 to 2	0.33±1.11 (−2.0 to 1.7)	0.48±0.84 (−1.0 to 1.8)
S_{aO_2} <90% (T90) (min)	Night 1	90.81±118.96 (0.0 to 361.0)	49.93±48.94 (4.7 to 191.6)
	Night 2	93.41±99.74 (2.0 to 301.5)	82.05±76.46 (1.4 to 287.8)
	Δ night 1 to 2	2.61±39.09 (−82.2 to 81.5)	33.95±53.49 (−34.6 to 173.7)

Data are presented as mean±SD (with ranges where appropriate), unless otherwise stated. In the placebo group, the number of per protocol analysis subjects was 15 for both nights. In the BAY 2253651 group, the numbers of per protocol analysis subjects were 16 for night 1, and 15 for night 2. ESS: Epworth Sleepiness Scale; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; S_{aO_2}: arterial oxygen saturation; Δ: delta (difference).

Part A had a multicentre, randomised, parallel, double-blind, placebo-controlled, group comparison design with a single nasal dose (100 µg) of BAY 2253651. Participants were randomised to either 100 µg of BAY 2253651 intranasally or to a placebo nose spray and then went to sleep (night 2).

Part B was an open-label follow-up with 100 µg BAY 2253651 applied at home over 5 consecutive nights. Data from home pulse oximetry for the parameters "oxygen desaturation index (ODI) ⩾3%, all night"; "ODI ⩾4%, all night"; and "mean peripheral oxygen saturation (S_{pO_2})" were collected.

Participants were stratified (1:1) according to OSA severity (moderate OSA with AHI 15–30 *versus* severe OSA with AHI 31–50 events per h sleep) after the first PSG using an interactive voice/web response system (IxRS). For part A, the nasal sprays containing BAY 2253651 or corresponding placebo were identical in appearance (size, colour and shape). The packaging and labelling were designed to maintain blinding to the site staff as well as to the participants. The study data remained blinded until all clinical assessments have been completed, database lock and authorisation of data release according to standard operating procedures.

PSG was conducted and scored according to the recommendations from the American Academy of Sleep Medicine from 2007 (AASM 2007 Version B) and endophenotypes ("treatable traits") were determined [12–15].

Responder rates (where a responder was defined by the reduction of the AHI (0–4 h) from baseline ⩾50%) of the placebo and active arm were compared using a Bayesian approach. This study was planned to fulfil the go criterion if the posterior probability that the responder rate in the active arm is larger than the responder rate under placebo exceeds 0.95. On the assumption of a response rate of 0.10 to placebo and 0.40 to the active drug, 30 participants per treatment arm were needed to provide 87% probability to go. The sponsor terminated the trial for futility after data review of the first 30 subjects randomised.

34 participants (mean±SD age 63.4±8.5 years, 64.7% males) with recurrent moderate to severe OSA were randomised. Recruitment started on 13 August, 2018 and the last follow-up was at the 23 May, 2019.

Craniofacial phenotyping presented no relevant differences between AHI strata for parameters with strong relationship to OSA severity.

The responder rate was 1 (6.3%) for BAY 2253651 and 1 (6.7%) for placebo. There were no differences in any of the standard PSG parameters (all p>0.05) (table 1). The posterior probability that the responder rate under BAY 2253651 is larger than the responder rate under placebo equals 0.476. There were no overall group differences in endophenotype traits, but the mean of the peak inspiratory airflow during sleep was higher at baseline in those who had an improvement in their AHI with BAY 2253651 (defined as any reduction in AHI from baseline) *versus* those who did not (0.92±0.10 *versus* 0.74±0.12% wakefulness; p=0.005).

Due to early termination only nine subjects proceeded with the open label multiple dose study part B (5 nights), where no relevant changes from baseline were observed for the parameters "ODI ⩾3%, all night"; "ODI ⩾4%, all night"; and "mean S_{pO_2}".

Considering potential cardiovascular side-effects of potassium channel blockers, no relevant changes or adverse events were observed for local side-effects, heart rate, blood pressure, and ECG rhythm. One participant had a temporarily increased QT-interval 6 days after last intake of BAY 2253651 while taking Citalopram (but not during the intervention night).

A single dose of 100 µg BAY 2253651, applied nasally, did not lead to a reduction in AHI in people with moderate to severe OSA off CPAP. A limitation of our trial is the small sample size, as the trial was terminated early due to futility. Another limitation is missing data on actual drug delivery. While an effect on polysomnographic parameters of OSA can be ruled out with confidence (based on part A and B data), the trial was non-informative from a mechanistic point of view. A proof of mechanism trial with a chemically altered follow-up compound is currently recruiting patients (NCT04236440).

Finally, there were no major discernible differences in other polysomnographic or pulse oximetric parameters between the BAY 2253651- and placebo-treated patient groups. However, similar to other non-CPAP interventions and consistent with OSA endophenotyping concepts, those who have less collapsible pharyngeal airways at baseline may be more likely to respond favourably to pharmacotherapy. Lastly, BAY 2253651 was safe and well-tolerated in the treated group of OSA patients.

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This study was registered at Clinicaltrials.gov with identifier NCT03603678. Original data are available from the corresponding author upon reasonable request.

Author contributions: G. Weimann, S. Unger, R. Finger and C. Xing had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: T. Gaisl, C.D. Turnbull, G. Weimann, S. Unger, R. Finger, C. Xing, P.A. Cistulli, D.J. Eckert, J.R. Stradling and M. Kohler. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: T. Gaisl, G. Weimann, M. Kohler and S. Steinbach (professional medical writer). Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: T. Gaisl and S. Unger. Administrative, technical or material support: T. Gaisl, G. Weimann, R. Finger, C. Xing, J.R. Stradling and M. Kohler. Study supervision: G. Weimann, R. Finger, C. Xing and M. Kohler. Independent supervision, compliance regulations, data management and monitoring: PRA Health Sciences.

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