Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes

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SUMMARY

Reduced upper airway muscle activity during sleep is a key contributor to obstructive sleep apnea pathogenesis. Hypoglossal nerve stimulation activates upper airway dilator muscles, including the genioglossus, and has the potential to reduce obstructive sleep apnea severity. The objective of this study was to examine the safety, feasibility and efficacy of a novel hypoglossal nerve stimulation system (HGNS®; Apnex Medical, St Paul, MN, USA) in treating obstructive sleep apnea at 12 months following implantation. Thirty-one subjects (35% female, age 52.4 $\pm$ 9.4 years) with moderate to severe obstructive sleep apnea and unable to tolerate positive airway pressure underwent surgical implantation and activation of the hypoglossal nerve stimulation system in a prospective single-arm interventional trial. Primary outcomes were changes in obstructive sleep apnea severity (apnea–hypopnea index, from in-laboratory polysomnogram) and sleep-related quality of life [Functional Outcomes of Sleep Questionnaire (FOSQ)]. Hypoglossal nerve stimulation was used on 86 $\pm$ 16% of nights for 5.4 $\pm$ 1.4 h per night. There was a significant improvement ($P < 0.001$) from baseline to 12 months in apnea–hypopnea index (45.4 $\pm$ 17.5 to 25.3 $\pm$ 20.6 events h^{-1}) and Functional Outcomes of Sleep Questionnaire score (14.2 $\pm$ 2.0 to 17.0 $\pm$ 2.4), as well as other polysomnogram and symptom measures. Outcomes were stable compared with 6 months following implantation. Three serious device-related adverse events occurred: an infection requiring device removal; and two stimulation lead cuff dislodgements requiring replacement. There were no significant adverse events with onset later than 6 months following implantation. Hypoglossal nerve stimulation demonstrated favourable safety, feasibility and efficacy.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterised by repeated episodes of upper airway obstruction during sleep. This disease is associated with substantial cardiovascular morbidity and mortality, endocrine disturbances, daytime somnolence, decreased quality of life, performance deficits, and motor vehicle crashes. OSA is common, affecting over 100 million individuals world-wide, with increasing prevalence due to obesity and ageing (World Health Organization, 2012; Young *et al.*, 1993). Positive airway pressure is the first-line treatment because it eliminates disordered breathing events (Gay *et al.*, 2006); however, at least 30–40% of patients have low adherence (Kribbs *et al.*, 1993; Weaver and Grunstein, 2008). Reported outcomes for treatment alternatives are often based on short-term (6 months or less) assessments, leaving open the important question of longer-term outcomes.

A number of factors contribute to OSA pathogenesis, including decreased tone during sleep in the upper airway dilator muscles, especially the genioglossus (White, 2005). This notion has led to investigations of electrical stimulation of the genioglossus using intramuscular or transcutaneous electrodes. While these studies demonstrated improvements in airway patency and OSA severity (Kezirian *et al.*, 2010), muscle stimulation disrupted sleep because of sensory phenomena. As a result, direct electrical stimulation of the motor nerve innervating the genioglossus muscle, the hypo-glossal nerve (HGN), has been explored as an alternative (Eisele *et al.*, 1997; Goding *et al.*, 1998; Schwartz *et al.*, 2001). Schwartz *et al.* (2001) showed the benefit of this approach, demonstrating that chronic HGN stimulation in patients with OSA decreased the frequency of obstructed breathing events without arousals from sleep. Despite this early promise, a number of device technical failures (Schwartz *et al.*, 2001), primarily electrode breakage and sensor failure, prevented further development.

These technical issues have been addressed in a new-generation implantable HGN stimulation (HGNS) therapy system (HGNS®; Apnex Medical, St Paul, MN, USA) that has recently been developed to explore further this OSA treatment modality. Early clinical trials in Australia and the USA have demonstrated improvements in airway patency and airflow without causing arousals from sleep (Schwartz *et al.*, 2012) Outcomes at 6 months in an Australian cohort following implantation suggested favourable safety, compliance and effectiveness.(Eastwood *et al.*, 2011) The present study extends these observations to report the safety, compliance and efficacy of the HGNS system at 12 months following implantation in the combined Australian and American cohorts. The purpose was to determine whether or not the therapy was associated with sustained benefit, which would be required for this therapeutic approach to be viable.

MATERIALS AND METHODS

Study design and participants

Study methods have been described previously (Eastwood *et al.*, 2011). A single-arm, open-label study was undertaken at four Australian and four USA clinical trial sites. Inclusion criteria included: moderate to severe OSA; documented failure of positive airway pressure; age 21–70 years; and body mass index (BMI) ≤ 40 kg m^{-2} (Australia) or ≤ 37 kg m^{-2} (USA). On the baseline sleep study (polysomn-ogram), subjects were required to have an apnea–hypopnea index (AHI) of 20–100 events h^{-1}, with at least 15 events h^{-1} occurring in non-rapid eye movement (REM) sleep; after an initial enrollment period ($n = 5$), all subjects were required to have a predominance of hypopneas ($\geq 80\%$) of the sum of apnea and hypopnea events. Exclusion criteria included: prior upper airway surgery; markedly enlarged tonsils; uncontrolled nasal obstruction; severe retrognathia; >5% central or mixed apneic events; incompletely treated sleep disorders other than OSA; and major disorder of the pulmonary, cardiac, renal or nervous systems.

HGNS system

The HGNS system consisted of an implantable neurostimu-lator connected to a unilateral (generally right-sided) stimu-lation lead and two respiration sensing leads (Fig. 1). The respiration sensing leads were tunnelled and placed subcu-taneously to monitor respiration from changes in thoracic bioimpedance. A software algorithm controlled the delivery of HGN electrical stimulation so that stimulation began just prior to and continued throughout inspiration, but was switched off during expiration. The flexible stimulation lead cuff was designed to distribute the stimulation field uniformly and to limit contact pressure in order to minimise the likelihood of nerve injury. Individualised therapy settings were pro-grammed into the neurostimulator, but participants could control limited aspects (start, stop and pause) with a handheld controller.

The HGNS system was implanted under general anaes-thesia. Briefly, the cuff of the stimulation lead was placed on the main trunk of the HGN distal to branches innervat-ing the tongue's retractor muscles to ensure predominant activation of the protrusors. Due to variability in HGN anatomy, the final cuff placement was determined by intraoperative response of the upper airway to stimulation, visualised using fluoroscopy. The stimulation lead body was then tunnelled deep to the platysma muscle in the neck to the neurostimulator, which was implanted in an ipsilateral infraclavicular subcutaneous pocket. From the pocket, two subcutaneous respiratory sensing leads were placed by tunnelling subcutaneously toward the midline and then along each costal margin.
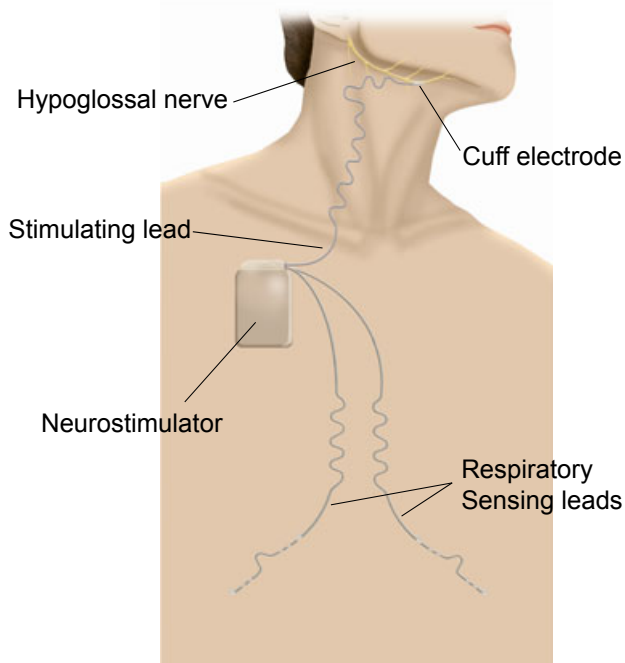
Figure 1. The implanted components of the HNS system include a neurostimulator that delivers safe levels of electrical stimulation to one HGN via a stimulation lead with a distal cuff electrode. Respiration sensing leads detect inspiration using bioimpedance, so that the system delivers stimulation synchronous with inspiration.

Polysomnograms (sleep studies)

All subjects underwent a full-night, in-laboratory polysomnogram at the respective centre prior to implantation (Baseline Night). Data were scored by a central core laboratory (Clinilabs, New York, NY, USA). The 1999 American Academy of Sleep Medicine apnea and hypopnea definitions were used (1999), except that a 4% oxygen desaturation was required for hypopneas (i.e. modified Chicago criteria). Sleep staging was consistent with the 2007 American Academy of Sleep Medicine conventions (Iber *et al.*, 2007).

After allowing approximately 1 month following implantation for healing, each subject underwent a titration polysomnogram, during which stimulation settings (e.g. pulse width, frequency, current) were adjusted to levels that consistently abolished inspiratory airflow limitation. Therapy was then commenced nightly at home. Downloadable utilisation data were stored in the devices. In-laboratory sleep studies were performed at 3, 6 and 12 months post-implantation. Information regarding at-home stimulation utilisation was stored on the device and downloaded.

At baseline, and at 6 and 12 months post-implantation, subjects completed five questionnaires: the Functional Outcomes of Sleep Questionnaire (FOSQ), assessing the impact of excessive sleepiness on activities of daily living (Weaver *et al.*, 1997); the Epworth Sleepiness Scale, measuring subjective daytime sleepiness (Johns, 1991); the Calgary Sleep Apnea Quality of Life Index, measuring within-patient change in sleep apnea-related quality of life in response to therapeutic intervention (Flemons and Reimer, 2002); the Pittsburgh Sleep Quality Index, assessing sleep quality and sleep disturbance retrospectively over a 1-month period (Buysse *et al.*, 1989); and the Beck Depression Inventory, rating the level of depressive symptoms (Lasa *et al.*, 2000).

Effectiveness, compliance and safety endpoints

The primary effectiveness endpoints were the mean change in AHI and FOSQ total score. Secondary effectiveness endpoints included the mean change for other polysomnographic and symptom measures. The usage endpoints were the proportion of nights with use and nightly hours of use. The primary safety endpoint was the rate of freedom from serious adverse events at implantation, and at 6 and 12 months post-implantation. All adverse events were reported. Adverse events were deemed serious if they resulted in: patient death; life-threatening illness or injury; permanent impairment of body structure or function, or medical or surgical intervention to prevent this; or in-patient hospitalisation or prolongation of existing hospitalisation.

Statistical analysis

There were no human clinical data to perform formal sample size calculations *a priori*. Analyses were by an intention to treat analysis, such that all subjects with a post-implantation efficacy study were included in the analysis. For subjects without data at the 6- ($n = 2$) and/or 12- ($n = 3$, including 1 due to explant) month time points, the most recent available data were carried forward for statistical analysis. Repeated-measures regression models were used to assess statistical differences in outcomes between visits. In cases where the normality assumption was violated ($P < 0.05$ from a Shapiro–Wilk test for normality of the studentised residuals), non-linear transformations (including logarithmic) were explored to produce models with improved fits. A linear model was used to compare the 12-month AHI values between those with a BMI $\leq$ and >35 kg m^{-2}. *P*-values were adjusted by the Sidak–Holm method to control for multiple comparisons. Statistical analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC, USA). Data are presented as mean $\pm$ SD and/or median and percentiles, where appropriate. *P*-values <0.05 were considered statistically significant.

Adverse event profiles for the intraoperative period, perioperative period, and at 6 and 12 months post-implantation were calculated to estimate the rate of freedom from incident system- (device or therapy) or procedure-related serious adverse events, using the Kaplan–Meier method of time-to-event analysis.

Ethical considerations

The study protocol was reviewed and approved by the Therapeutic Goods Administration and the Ethics Committees

at each participating Australian site. It was also reviewed and approved by the United States Food and Drug Administration and the institutional review board at each participating United States site. Adverse events were adjudicated by an independent Clinical Events Committee. An independent Data Safety Monitoring Committee provided ethical and scientific review of the study. Subjects provided written informed consent prior to their involvement in any study procedure. The trial was registered at ClinicalTrials.gov as NCT01186926 (Australian study) and NCT01211444 (US study).

Role of the funding source

The study was funded by Apnex Medical (Minneapolis, MN, USA). The academic authors are responsible for study design; the collection, analysis and interpretation of data; writing of the manuscript; and the decision to submit the paper for publication. Apnex Medical provided assistance with study design and data analysis, and reviewed the manuscript prior to submission; however, the academic authors are fully responsible for its contents.

RESULTS

Thirty-two subjects were implanted, but one requested explant (performed without incident) prior to activation and was excluded from further analyses. Of the 31 subjects with device activation, 11 (35%) were female, and age was 52.4 ± 9.4 years. BMI was 32.4 ± 3.6 kg m^{-2}. Most (28/31, 90%) were non-Hispanic Caucasian, and one subject each had race/ethnicity of Hispanic Caucasian, Black/African American and multiracial. At baseline, all subjects had moderate to severe OSA, with reduced deep sleep and REM sleep (Table 1) and related symptoms (Table 2).

The AHI decreased from 45.4 ± 17.5 to 25.3 ± 20.6 events h^{-1} ($P < 0.001$), and was stable at 12 months relative to 6 months post-implantation ($P = 0.56$; Fig. 2; Table 1). There were similar findings between these assessments for other measures of disordered breathing events, arousal index and sleep architecture (increased REM sleep). Seventeen (55%) participants achieved a response to treatment, using the most common definition for OSA surgical treatment success: an AHI decrease of ≥50% to <20 events h^{-1} (Sher *et al.*, 1996). Fifteen (48%) had a ≥50% AHI decrease to <15 events h^{-1}. Two (6%) had a ≥50% AHI decrease to 20–25 events h^{-1}.

All symptom and quality of life measures improved at 12 months following implantation, with no significant change from outcomes at 6 months (Table 2).

Subjects with BMI ≤ 35 kg m^{-2} (68%, 21/31) demonstrated a significantly greater AHI reduction and improvement in symptoms at 12 months that was not seen in the subgroup with a BMI > 35 kg m^{-2} (Fig. 3). For the subjects with a BMI ≤ 35 kg m^{-2}, AHI decreased from 43.9 ± 17.4 to 18.7 ± 17.0 events h^{-1} ($P < 0.001$); 14 (67%) had a 50% AHI decrease to <15 events h^{-1}. There were no statistically

significant changes in the group with a BMI > 35 kg m^{-2}, although the study was not adequately powered to rule out a change in AHI.

Following the month allowed postoperatively for healing, subject usage data were available for 266 ± 81 (median 272) nights (range 53–377), excluding days for which therapy
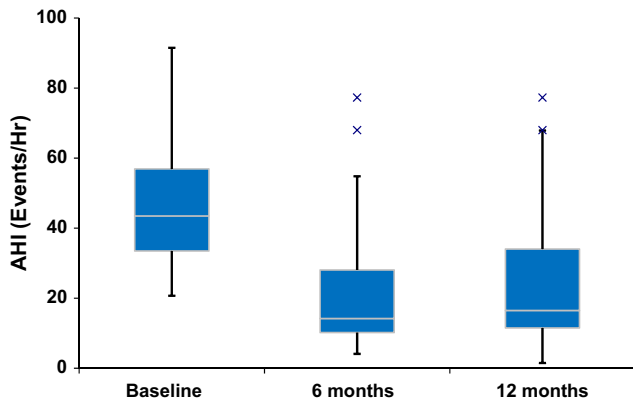
Table 1 Polysomnogram measures

Parameter	Baseline	6 months	12 months***
AHI (events h^{-1})	45.4 (17.5)	20.8 (17.6)*	25.3 (20.6)*
Apnea index (events h^{-1})	4.6 (6.3)	1.5 (2.2)*	3.2 (5.9)**
Hypopnea index (events h^{-1})	40.8 (15.3)	19.4 (16.6)*	22.1 (17.9)*
Arousal index (events h^{-1})	44.3 (17.7)	24.4 (13.2)*	27.5 (13.4)*
Respiratory arousal index	31.4 (18.4)	11.9 (11.9)*	14.4 (12.4)*
ODI4% index (events h^{-1})	20.9 (17.3)	10.7 (17.1)*	15.7 (19.6)*
Total sleep time (min)	346.4 (71.6)	355.2 (52.9)	362.7 (55.9)
Sleep efficiency (%)	77.2 (12.6)	82.8 (10.9)**	82.6 (10.2)**
% N1	29.3 (11.2)	20.5 (10.2)*	21.8 (10.3)*
% N2	48.8 (7.9)	52.3 (10.2)	50.6 (8.4)
% N3	9.3 (7.7)	10.9 (8.9)	11.9 (8.9)
% REM	12.6 (6.5)	16.1 (5.7)**	16.4 (5.0)**

AHI, apnea–hypopnea index; ODI, oxygen desaturation index; REM, rapid eye movement.
All values are presented as mean (SD). *P*-values are all compared with baseline, using data only for subjects with data at each respective time point.
*$P < 0.001$.
**$P < 0.05$, but >0.001.
***P-values for all comparisons of 12-month versus 6-month results are >0.10, except for ODI4% index ($P = 0.09$).

Table 2 Symptoms and quality of life measures

Scale	Baseline	6 months	12 months***
FOSQ	14.2 (2.0)	16.8 (2.4)*	17.0 (2.4)*
ESS	12.1 (4.6)	8.3 (3.6)*	7.9 (3.8)*
SAQLI	3.1 (1.1)	4.8 (1.4)*	4.9 (1.4)*
PSQI	9.9 (3.2)	8.3 (4.3)	7.8 (4.3)**
BDI	15.7 (9.0)	8.5 (7.8)*	9.1 (8.2)*

FOSQ, Functional Outcomes of Sleep Questionnaire; ESS, Epworth Sleepiness Scale; SAQLI, Sleep Apnea Quality of Life Index; PSQI, Pittsburgh Sleep Quality Index; BDI, Beck Depression Inventory.
All values are presented as mean (SD). *P*-values are all compared with baseline, using data only for subjects with data at each respective time point.
*$P < 0.001$.
**$P < 0.05$, but >0.001.
***P-values for all comparisons of 12-month versus 6-month results are >0.60.

Figure 2. Box and whisker plot of the apnea–hypopnea index (AHI) at baseline, and at 6 and 12 months post-implantation. The median values are noted by horizontal white lines, and the boxes represent the intraquartile range. The whiskers represent the 1.5× intraquartile range (or the minimum or maximum value if <1.5× the intraquartile range). X represents outlier values.
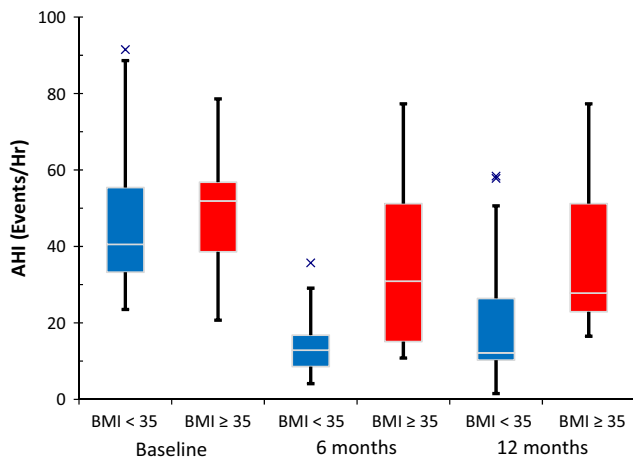

Figure 3. Box and whisker plot of the apnea–hypopnea index (AHI) at baseline, and at 3, 6 and 12 months post-implantation, shown separately for body mass index (BMI) ≤35 kg m^{-2} and >35 kg m^{-2}. The median values are noted by horizontal white lines, and the boxes represent the intraquartile range. The whiskers represent 1.5× the intraquartile range (or the minimum or maximum value if <1.5× the intraquartile range). X represents outlier values.

was known to be discontinued, often due to lack of objective and/or subjective efficacy. Therapy was used a mean of 86 ± 16% of nights (range 42–100%) for 5.4 ± 1.4 h night^{-1} (range 2.7–8.4 h). There were no deaths in the study and no unanticipated adverse device effects. Four devices were explanted (one with request prior to activation, two due to lack of sufficient objective and subjective effectiveness, and one due to device infection). Two participants had dislodgement of the stimulation lead cuff within 2 weeks of implantation (without HGN damage) and had replacement surgery accomplished without sequelae. One subject was readmitted to the hospital for psychological disturbance related to a combination of self-discontinuation of anti-depressant

medications and prescription of opioids for postoperative pain control (although almost all patients used narcotics in the recovery period, the use of narcotics in this patient was felt to contribute to psychological disturbance). At least one adverse event related to the implantation procedure or therapy occurred in 71% (22/31) and 32% (10/31), respectively, but only 3/31 (10%) experienced serious adverse events related specifically to therapy. The most common procedure-related events were numbness/pain at the incision sites (35%, 11/31), and the most common therapy-related events were tongue abrasions (55%, 17/31) caused by movement of the tongue over mandibular dentition. These abrasions were of short duration and self-limited, and they were successfully treated with plastic dental guards. Most adverse events resolved completely, and the rate of freedom from system (device or therapy) or procedure-related adverse events at 12 months was 71% (22/31 subjects). The adverse events persisting at 12 months were incisional numbness/pain (8/31 subjects, 26%) and intermittent tongue soreness (3/31, 10%). Only one adverse event had onset later than 6 months following implantation: incisional numbness that resolved spontaneously after 2 days.

DISCUSSION

The HGNS system is a safe, feasible and effective treatment for individuals with moderate to severe OSA who are unable to use positive airway pressure therapy. At 12 months following implantation, there were substantial improvements in objective measures of OSA severity and sleep disturbance as well as subjective metrics of daytime functioning, demonstrating that prior preliminary results (Eastwood *et al.*, 2011) were robust over time in a larger sample. Furthermore, these improvements in symptom and quality of life measures were not only statistically significant but also clinically meaningful, based on previous studies using these instruments. The subjective measures mirror the objective improvements in sleep architecture seen on polysomnography of improved sleep architecture. Subjects with BMI > 35 kg m^{-2} appeared to respond less favourably, perhaps because of fat deposition within tissues surrounding the upper airway (Nashi *et al.*, 2007; Schwab *et al.*, 2003). These findings are broadly consistent with previous studies of this and earlier technologies (Eisele *et al.*, 1997; Goding *et al.*, 2012; Schwartz *et al.*, 2001, 2012; Van De Heyning *et al.*, 2012).

Therapy usage was high, comparing favourably with positive airway pressure adherence (Kribbs *et al.*, 1993). The HGNS system was safe, with few serious adverse events, resolution of most adverse events over time, and only one minor adverse event with onset later than 6 months after therapy initiation.

The feasibility of chronic HGNS as a potential OSA therapy has been described previously by Schwartz *et al.* (2001). The system used in their study was safe but had technical problems (Eisele *et al.*, 2003; Goding *et al.*, 1998; Schwartz *et al.*, 2001). Numerous design differences were incorporated

into the present HGNS device to overcome these problems. Principal among these was the development of a cuff electrode designed to surround the HGN branch safely and securely, and the development of a bioimpedance-based respiratory sensing system.

Outcome evaluation in most surgical trials is limited to 6 months following surgery. Longer-term assessments are essential and clinically meaningful, and the stability of the results is clinically meaningful. Two studies have reported 12-month outcomes in HGNS, both in populations with lower BMI. Mwenge *et al.* (2013) reported similar changes in AHI and subjective outcomes in a smaller, single-centre trial utilising a different technology. At a recent scientific meeting (Sleep, 2013), Strollo *et al.* (2013) presented similar AHI changes in a multi-centre, pivotal trial of yet another HGNS technology, and full presentation of those results in publication is forthcoming. The reproducibility of these findings suggests that HGNS may be a viable treatment option in OSA, but because HGNS does not alleviate OSA in all subjects, there is a potential for improvement in treatment selection or additional benefit from adjunctive interventions.

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AUTHOR CONTRIBUTIONS

EJK: study design, literature search, data analysis and interpretation, writing, final approval. GSG: study design, data collection, manuscript review. AM: study design, data synthesis, review of raw data, data interpretation, study site coordination, and manuscript review. FOD: data collection and interpretation, manuscript review. GZ: data collection. JRW: study design, data collection and interpretation, manuscript review. PGC: data collection, manuscript review. PLS: developed concept for neural stimulation, monitored selection of study subjects, reviewed raw data. ARS: study design, data monitoring and analysis, and formulation of study findings and conclusions. JHW: data collection, analysis, and interpretation; manuscript review. KJM: data collection, analysis, and interpretation; manuscript review. TH: study design and data collection. SYP: data collection. DMC: subject recruitment, data acquisition, data analysis, and manuscript review and approval. MCC: data collection, manuscript review. CEP: data collection, manuscript review. CI: data collection, data interpretation. PRE: study design, data collection, data analysis and interpretation, manuscript writing and review. DRH: study design, data collection, data interpretation, manuscript writing. MB: data collection, data analysis, manuscript writing.

CONFLICTS OF INTEREST

EJK: Apnex Medical (Medical Advisory Board, consultant); ReVENT Medical (Medical Advisory Board); ArthroCare (consultant); Medtronic (consultant); Pavad Medical (consultant). GSG: Apnex Medical (consultant). AM: consulting/research income from Philips, Apnex, Apnicure, Pfizer, SHC and SGS, but has relinquished all outside personal income since May 2012. GZ: grants/research support (Abbott, Actelion, Ancile, Apnex, Arena, Astra-Zeneca, Aventis, Banyu, Biomarin, BMS, Catalyst, Cephalon Inc., CHDI, Elan, Epix, Eisal, Elminda, Evotec, Forest, Galderma, Glaxo-SmithKline, Gilead, H. Lundbeck A/s, King, Merck and Co., National Institutes of Health, Neurim, Neurocrine Biosciences, Naurex, Neurogen, Novo Nordisk, Organon, Orphan Medical, Otsuka, Pfizer, Predix, Respironics, Saladax, Sanofi-Aventis, Sanofi-Synthelabo, Schering-Plough, Sepracor, Shire, Somaxon, Takeda Pharmaceuticals North America, Targacept, Teva, Thymon, Transcept, UCB Pharma, Ultragenyx, Predix, Venda, Wyeth-Ayerst Research; consultant: Acorda, Actelion, Alexza, Arena, Aventis, Biovail, Boehringer-Ingelheim, Cephalon, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Jazz, King Pharmaceuticals, Ligand, McNeil, Merck, Neurocrine Biosciences, Organon, Pfizer, Purdue, Renovis, Sanofi-Aventis, Select Comfort, Sepracor, Shire, Somnus, Takeda Pharmaceuticals, Vela, Wyeth; honoraria: Neurocrine Biosciences, King Pharmaceuticals, McNeil, Sanofi-Aventis, Sanofi-Synthelabo, Sepracor, Takeda Pharmaceuticals, Vela Pharmaceuticals, Wyeth-Ayerst Research; ownership, directorship: Clinilabs Inc., Clinilabs IPA, Clinilabs Physician Services. PLS: Apnex Medical (Medical Advisory Board). ARS: Apnex Medical (Scientific Advisory Board). TH: Apnex Medical (Medical Advisory Board, compensated surgical proctor). SYP: Apnex Medical (compensated surgical proctor). CEP: Apnex Medical (consultant). CI: Apnex Medical (salary support). PRE: Apnex Medical (Medical Advisory Board, consultant). DRH: Apnex Medical (Medical Advisory Board). MB: Fisher & Paykel (attendance at Clinical Research Forum), Bird Pty Ltd (salary support for research assistant for investigator-driven research project), ResMed (provision of equipment for investigator-driven research project),sponsored clinical trials with no direct monies received (Actelion, Boehringer-Ingelheim, Apnex Medical, GlaxoSmithKline, Novartis, Hunter Immunology, Pearl Therapeutics, Sanofi-Aventis).

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