Effect of custom-made vs thermoplastic heat-molded mandibular advancement devices for Obstructive Sleep Apnea after 12 months: A randomized non-inferiority trial

INTRODUCTION

Obstructive sleep apnoea (OSA) is characterized by repetitive episodes of partial or complete pharyngeal obstruction during sleep.[1] OSA is one of the most frequent chronic diseases with both social and multiorgan consequences making it an economic burden for society. OSA durably impairs the quality of life of patients and their bedpartners and is associated with co-morbidities including hypertension, arrhythmias, stroke, coronary heart disease and metabolic dysfunction.[1]

Continuous positive airway pressure (CPAP), the first-line therapy for OSA, requires high adherence to be effective in terms of symptom improvement and reduction of the burden of co-morbidities.[2] Such adherence is difficult to achieve in the long term and mandibular advancement devices (MADs) have emerged as the leading alternative to CPAP. MAD and CPAP are similarly effective on symptoms, quality of life[3,4] and in attaining reductions in blood pressure and cardiovascular morbidity.[5,6] Although CPAP has a greater effect on apnoea–hypopnea index (AHI) reduction, adherence is better with MAD explaining the comparable mean disease alleviation achieved by the two treatment modalities.[4]

Despite good tolerance and efficacy, there are still barriers limiting the widespread use of MAD and its acceptance in OSA routine clinical practice.[7] Various different MAD designs currently exist and constantly emerge on the market without clear evidence regarding the best technical choice and the cost-effectiveness compromise.[8] Titratable two-piece custom-made MADs are considered the gold standard in clinical guidelines but at the price of higher costs and treatment delays for manufacture to customized specifications. Also, the MAD titration (adjustment of the degree of protrusion to optimize therapy) procedures are poorly standardized and the process can last several months with difficulties in predicting long-term effectiveness. Thermoplastic two-piece MADs constructed of a material that becomes moldable when warmed by immersion in hot water,[7] recently became titratable and might offer relatively cheap devices for testing efficacy in a given patient and to provide a fast-track treatment pathway before prescription of a more expensive two-piece custom-made MAD for long term use.[9] Such a paradigm merits being tested in a randomized controlled head-to-head trial. This study was a pragmatic, multicenter, parallel-group randomized controlled trial to determine whether the

two-piece thermoplastic heat-molded titratable MAD (ONIRIS; ONIRIS SAS, Rueil Malmaison, France) is non-inferior to the two-piece custom-made acrylic titratable MAD (TALI; ONIRIS SAS, Rueil Malmaison, France) in patients with OSA refusing or not tolerating CPAP. The primary outcome was efficacy response at 2 months and secondary outcomes included tolerance and adherence at 2 months has been previously describe.[10] Results demonstrated a clear non-inferiority of the thermoplastic heat-molded titratable MAD (ONIRIS). The non-inferiority was true not only for the primary outcome (rate of response) but also for parameters of OSA severity (AHI), compliance, patient-centered outcomes including symptoms and quality of life, and co-morbidities (blood pressure reduction). The Authors conclude that such a thermoplastic heat-molded titratable MAD might represent a simple, cheaper, and clinically feasible method of identifying patients likely to benefit from long-term MAD therapy before prescription of a more costly device.

However, the thermoplastic MAD studied has a lifespan of 2 years and we can wonder about its long-term use which could allow a more efficient alternative to custom-made MAD. To answer this question, it was necessary to have longer-term data and therefore patients were asked to wear the device for 1 year with outcomes, including tolerability, efficacy and compliance assessed at 12 months. The present article exposes these results.

MATERIALS AND METHODS

Study design and participants

This trial was a multicenter, randomized, controlled, open study. The study population consisted of adults (> 18 years) with severe OSA refusing or not tolerating CPAP without dental, periodontal or joint contra-indications and never treated with MADs. According to French Pulmonology Society[11] severe OSA was define as AHI ≥ 15.h-1 with severe daytime sleepiness associated to at least two of the following criteria: severe and daily snoring, gasping or choking sensations, unrefreshing sleep, fatigue, awareness falls and nocturia. Patients were recruited from private practice, clinics, hospital and university hospital centers.

The main exclusion criteria were severe psychiatric or neuromuscular disorders (at the discretion of the investigator); more than 20% of central sleep apnoea and hypopnea; severe OSA with AHI ≥ 30.h-1 associated to coexistent sleep disorders (narcolepsy, hypersomnia, severe Restless legs syndrome) ; BMI > 30kg/m2; ongoing or scheduled orthodontic treatment; untreatable vomiting reflex, pregnant or breastfeeding women; epileptic patients, inability to give informed consent, patient included in an ongoing clinical study; patient not covered by the French health insurance system.

The trial was registered at www.clinicaltrials.gov, NCT02348970. The protocol was approved by the institutional review board for each center, and all participants provided written informed consent. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Randomization and masking

Patients were first recruited by sleep specialists in private practice or in hospital center. If they met the inclusion criteria patient were seen by a prosthesis specialist to evaluated dental, periodontal or joint contra-indications. In absence of contra-indications patients were randomly assigned (1:1) to one of the two treatment groups (custom-made MAD (TALI®) or thermoplastic heat molded MAD (ONIRIS®)) with minimization to balance assignment by study center and by initial apnea-hypopnea index (AHI) severity (two level: AHI>30, AHI<=30). Study treatment assignment information was provided by the mean of the e-CRF to the prosthesis specialist (dentist or ENT) at the time of the first connection. Investigators and patients were not masked to treatment assignment.

Procedures

ONIRIS® (ONIRIS SAS – Rueil Malmaison – France) is a bi-bloc titrable thermoplastic MAD, made of two stiff gutters heat-molded on dental arches, coupled by two adjustable connecting rods allowing to set the mandibular advancement by steps of 1mm and a freedom of opening jaw movement. TALI® (ONIRIS SAS – Rueil Malmaison – France) is a bi-bloc titrable acrylic custom-made MAD allowing to set the mandibular advancement by steps of 1mm and a freedom of opening jaw movement.

Fifteen days after randomization patient were seen by the prosthesis specialist to set-up the MAD. MAD set-up was defined as study starting point. Patients were then asked to wear the MADs each night during sleep for the duration of the study (12 months). During the study patients were seen for follow-up visits by the prosthesis specialist at 15, 30 and 45 days and at 6 and 12 months to perform if needed MADs titration and to assess compliance, snoring intensity and arterial pressure. At 60 days and 12 months patients were seen by the sleep specialist and ambulatory PG or PSG was performed to evaluate AHI, AI and HI. In addition, the following parameters were also monitored snoring intensity; Epworth's sleepiness score; Pichot fatigue and depression scores, quality of life; compliance to treatment (self-reported); nature, frequency and intensity of adverse events; arterial pressure.

Outcomes

The primary efficacy endpoint (responder at 2 months defined by at least 50% decrease from baseline in AHI or an AHI<10.h-1) and secondary endpoints have been previously described.[10]

This paper only focuses on results at 6 and 12 months.

Efficacy endpoints at 12 months included responder rate, AHI per hour; Epworth's sleepiness score; Pichot's fatigue and depression scores; snoring intensity as measured on visual analog scale; health-related quality of life evaluated by SF12 form and arterial pressure.

Adherence to treatment evaluation was based on patients' self-assessment regarding the use of the device (number of nights per week and number of hours per night). Adherence results were classified in 3 classes: poor adherence when MAD was used less than 50% of the night, good adherence when MAD was used between 50% to 85% of the night and excellent adherence when MAD was use more than 85% of the night.

Safety assessment consisted of monitoring and recording of adverse events including serious adverse events and adverse events. Events were coded according to MedDRA version 10.8. Dental and temporomandibular joint impact at 6 and 12 months was evaluated by the dentist during a clinical examination and by comparison of the patient's dental arch to the original plaster model made on D-15. In case of impact, the intensity was evaluated by the patient and the dentist and only the most severe data was kept for the analysis.

Statistical analysis

Rational regarding the number of included patients has been previously been described[10] and it was concluded that a total of 162 evaluable patients (81 in each treatment group) were needed to satisfy the non-inferiority hypothesis.

In the present study the intention to treat (ITT) population included all randomized patients. The tolerance population (TOL) included all randomized patients who used the device at least once. The per-protocol population (PP) included all randomized patients who used the device at least once during the 2 months of follow-up with no major deviation regarding the established protocol such as non-compliance with major inclusion and exclusion criteria, no assessment of the primary endpoint at 2-month follow-up visit (except for patient reporting a lake of efficacy in-between).

Responder rate at 12 months was analyzed following a non-inferiority hypothesis (non-inferiority margin was defined as a difference between groups of 20%) on the PP population using two modalities: complete case and last observation carried forward (LOCF). In the latter, missing data at 12 months were replaced by the last available data or set as failure if the patient was excluded from the study due to treatment failure before 2 months. To confirm effects observed on the PP population further analysis using the 2 same modalities were done on the TOL population.

Secondary efficacy endpoints were analyzed on the TOL population using bilateral test with an alpha set at 0,05. Intra group evolution of secondary efficacy endpoint was analyzed through Cochran-Mantel-Haenszel test and comparison between groups was performed using a Student’s t test. These analyses were done using complete case, LOCF and Mixed-Effect Model Repeated Measure (MMRM) modalities. In the

MMRM analysis the following effects were considered: the parameter at baseline, the time point, the treatment group, the treatment group and time point interaction and the patient random factor.

RESULTS

Participants

Out of the 211 initially identified eligible patient, 198 patients were randomized to either ONIRIS® group (n=98) or TALI® group (n=100). The 13 non-randomized patients were excluded for the following reasons: study thought to be too restrictive (n=1); dental, periodontal or joint contra-indications (n=7); consent withdrawal (n=1); lost to follow-up (n=3); impossibility to attend follow-up visits (n=1). Out of the 198 severe OSA patients refusing or not tolerating CPAP, 8 patients (6 in the ONIRIS group and 2 in the TALI group) never used the treatment. Consequently, the TOL population included 190 patients. At 2 months, 34 patients were excluded from the TOL population due to major deviation regarding the established protocol. Consequently, the per-protocol population consisted of 156 patients: 69 in the ONIRIS® group and 87 in the TALI group. At 12 months, 60 additional patients were excluded, leaving 38 patients in the TALI® group and 30 patients in the ONIRIS® group (See Figure 1).

Baseline characteristics

Baseline demographics and clinical characteristics for tolerance population (TOL) and per-protocol population (PP) are exposed in Table 1. In the PP, the 87 patients treated with TALI® MAD and included for analysis were 52.9 ±12.2 years old, 77% (n=67/87) were men, with a mean BMI of 25,91 ±2.85 kg/m2. The indications for MAD treatment was CPAP refusal for 33 (37.9%) patients and CPAP intolerance for 54 (62.1%) patients. The 69 patients treated with ONIRIS® MAD and included for analysis were 49.3 ±11.2 years old, 72.5% (n=50/69) were men, with a mean BMI of 25,86 ± 2.71 kg/m2. The indications for MAD treatment was CPAP refusal for 29 (42%) patients and CPAP intolerance for 39 (56.5%) patients. At inclusion the mean AHI was 27.1 ± 19.9 and 26.1 ± 11.1 in TALI® and ONIRIS® groups respectively. In TALI® treatment group 61 (70.11%) patients had an AHI lower or equal to 30 and 26 (29.89%) had an AHI above 30. In ONIRIS® treatment group 47 (68.12%) patients had an AHI lower or equal to 30 and 22 (31.88%) had an AHI above 30. Whatever the population, more than 80% of patient were partially edentulous (at least one missing tooth) and the mean number of missing teeth was 3.9±3.2 in TALI® group and 3.4±2.4 in ONIRIS® group. Baseline demographics and clinical characteristics were well balanced between treatment groups (Table 1).

Efficacy outcomes

According to predefined criteria of success, 57.9% and 80% were successfully treated at 12 months for OSA in TALI® and ONIRIS® groups respectively. The difference does not exceed the non-inferiority

margin (difference 0.221; CI90% [0.0210; 0.4084], p=0.0015). Similar results were observed when the analysis was done using LOCF modality on the PP and TOL population (Table 2 and Figure 2).

After 12 months, analysis on the TOL population (LOCF modality) shows that both treatments enable to significantly improved AHI.h-1, SF12 PCS and MCS, Pichot's fatigue and depression scores, Epworth's score, snoring and systolic pressure in the subgroup of patient with an HTA at inclusion. No significant differences between the thermoplastic MAD (ONIRIS®) and the custom-made MAD (TALI®) were observed regarding these outcomes (Table 3, Figure 3 & Figure 4). It should be noted that similar results were observed using complete case and MMRM modality. At 12 months, diastolic pressure was also significantly improved from baseline in the ONIRIS® group but not in the TALI® group. However, no significant between the two was reported (Table 3 & Figure 4).

Significant improvements from baseline were also observed when analyzing AHI.h-1, Pichot's fatigue and depression scores, Epworth's score and snoring on the TOL population using complete case modality. However, this analyze did not show significant improvement from baseline for SF12 PCS outcome in both group and for SF12 MCS outcomes in ONIRIS® group. Nevertheless, no difference between groups was reported at 12 months using "complete case" modality.

At 12 months, patients were reporting using the MAD 88.9% of their sleep time in the TALI group and 89.1% in the ONRIS group (p=0.3734). Self-assessed adherence was rated as good or excellent for 91.9% of patient in TALI® group (Excellent: 83.8%; Good: 8.1%) and for 93.1% of patient in ONIRIS® group (Excellent: 82.8%; Good: 10.3%). No significant difference between groups was reported (p=1). When considering the TOL population using LOCF calculation adherence was significantly better in TALI® group (Good or excellent results: 88.1% vs. 71.9%; p=0.0093).

Adverse Events

No serious adverse event was reported in both treatment groups over the study.

At 12 months, only 2.5% and 3.4% of patients had significant dental or joint impact in TALI® and ONIRIS® group respectively (p=0.9076).

At 12 months, 86.1% of patient treated by TALI® and 73.3% of patient treated by ONIRIS® were reporting no discomfort (p=0.1231). Only 5,6% of patients treated with TALI MAD was reporting a discomfort that overcoming treatment benefits and in ONIRIS® group no patient was reporting a discomfort overcoming treatment benefits. During the ten-month follow-up period, only 23 discomforts was reported, 11 in the TALI group and 12 in the ONIRIS group. In the TALI group the most frequently reported discomforts were disagreement due to a TMJ pain (9.4%), a dry mouth (5.7%) or a tooth pain (3.8%). In the ONIRIS group the most frequently reported discomforts were disagreement due to a dry mouth (5.7%), volume in mouth (5.7%) and unspecified discomfort (5,7%).

Over the study period, 313 discomforts were reported of which 292 (92.7%) were reported during the first 2 months of adaptation and adjustment period. The most frequently (>10%) reported discomforts in TALI® group were dental discomfort (23.5%), dental pain (19.4%), joint pain (18.4%), dry mouth (12.2%) and muscular pain (9.2%). In ONIRIS® group the most frequently reported discomforts were disagreement due to MAD volume in mouth (21.7%), joint pain (17.4%), dental pain (17.4%), dental discomfort (15.2%), excessive salivation (13%), muscular pain (12%) and dry mouth (10.9%). Patients treated with ONIRIS® MAD were significantly reporting more disagreement due to MAD volume in mouth (21.7% vs. 4.1%; p<0.001) and excessive salivation (13% vs. 2%; p=0.044). For other reported discomfort, no difference was observed between groups.

Finally, significantly more patients in the TALI® group had MAD adjustments 93.9% vs. 84.8%; p=0.0412) and no difference was observed when the mean number of adjustments per patient is considered (2.7 ± 1.5 vs. 2.3 ± 1.5; p=0.1167).

DISCUSSION

This is the first randomized controlled trial providing a head to head comparison between a two-piece thermoplastic heat-molded titratable MAD (ONIRIS) and a two-piece custom-made acrylic reference titratable MAD (TALI) in patients with severe OSA refusing or intolerant to CPAP. This is also the first trial on a thermoplastic MAD with a 12-month follow-up period. Evaluation demonstrated clear non-inferiority of the thermoplastic heat-molded titratable MAD (ONIRIS). The non-inferiority was true not only for the primary outcome (rate of response) but also for parameters of OSA severity (AHI), patient-centered outcomes

including symptoms and quality of life, and co-morbidities (blood pressure reduction)., In addition, according to Mixed-Effect Model Repeated Measure analyzes, the improvements observed at 2 months on these parameter appear stable and durable during the follow-up period.

During the follow-up period, the frequency of side effects was equivalent in the two arms and was much lower than that reported during the first weeks of adjustment and adaptation. It is indeed interesting to note that 92.7% of the discomfort was reported during the first 2 months of treatment[10]. This underlines the importance of the adaptation period and of the MAD adjustments which, once made, allow a well-tolerated treatment in the long term.

To our knowledge, this is the first study to demonstrate the safety of a thermoplastic MAD compare to custom-made MAD as no significant difference appeared in dental and TMJ impacts, with low frequency in both arms.

CPAP and MADs are now considered as being nearly equally effective for treating moderate-to-severe sleep apnoea.[3,5,12] The main problem for more widely disseminating the prescription of MADs by routine sleep clinics is the huge heterogeneity in the design and complexity of the different devices available on the market. There is consensus in the sleep community towards the abandonment of prefabricated, non-adjustable, over-the-counter 'boil and bite' appliances that are associated with lower rates of efficacy, fall out more easily during the night and suffer from poor tolerance and lower adherence.[13–16] On the other end of the sophistication spectrum, two-piece custom-made, titratable MADs built by a qualified dentist still appear to be the gold standard according to clinical guidelines.[16] However, these MADs require several weeks to be manufactured, are more expensive and their efficacy is still difficult to predict. Experiencing failure of these high cost MADs even after titration might generate patient frustration and loss of cooperation for alternative treatments. Also, the degree of MAD sophistication influences cost-effectiveness ratios[15]; and finally, there is limited evidence as to which type of MAD is the best compromise in the treatment of mild-to-moderate OSA.

Our study evaluated the thermoplastic titratable ONIRIS MAD fitted by a qualified dentist which was immediately available to the patients. It is cheaper and allows treatment delays to be reduced compared with classic custom-made devices. In a bicentric cohort, Gagnadoux et al evaluated the efficacy of another titratable, thermoplastic MAD compared with a custom-made MAD.[9] They found no efficacy differences either during PSG or in clinical outcomes. However, the Gagnadoux study[9] was flawed by the usual limitations of observational studies while the robustness of our data is supported by a head-to-head comparison in a randomized controlled trial design. We clearly established that in patients with OSA refusing or not tolerating

CPAP, the thermoplastic heat-molded titratable MAD was non-inferior to the custom-made acrylic MAD in terms of the rate of response, reduction in indices of OSA severity, patient-centered outcomes and blood pressure improvement at 12 months.

Side effects were more frequent in the first couple of weeks of treatment with the thermoplastic MAD compared with the reference one[10]. This is essentially explained by differences in mouth encumbrance between the two appliances. Interestingly, over time, differences in reported side effects disappeared between the two arms. Moreover, reported adherence was high and above 6 hours per night in both arms with no statistical difference at 12 month .

CONCLUSION

Our quality pragmatic randomized controlled trial demonstrated that in patients with OSA refusing or not tolerating CPAP, a thermoplastic heat-moulded titratable MAD was non-inferior to a custom-made acrylic MAD at 12 months. Such a thermoplastic heat-moulded titratable MAD might represent a simple and cheaper, alternative to custom-made MAD for long-term OSA treatment.

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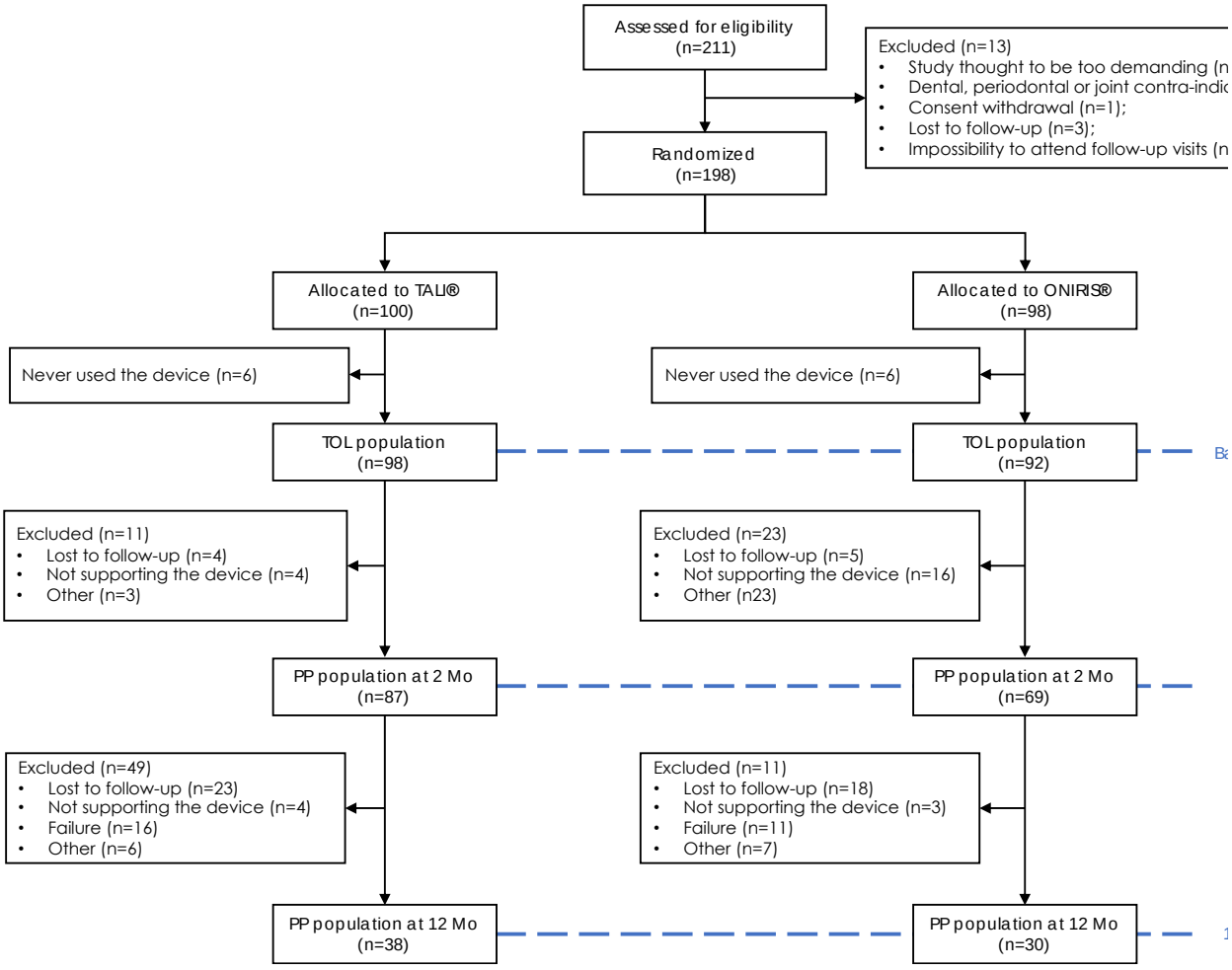

Figure 1. Patient flow-chart

ITT: Intention to treat population ; TOL : Tolerance population ; PP : Per-protocol population

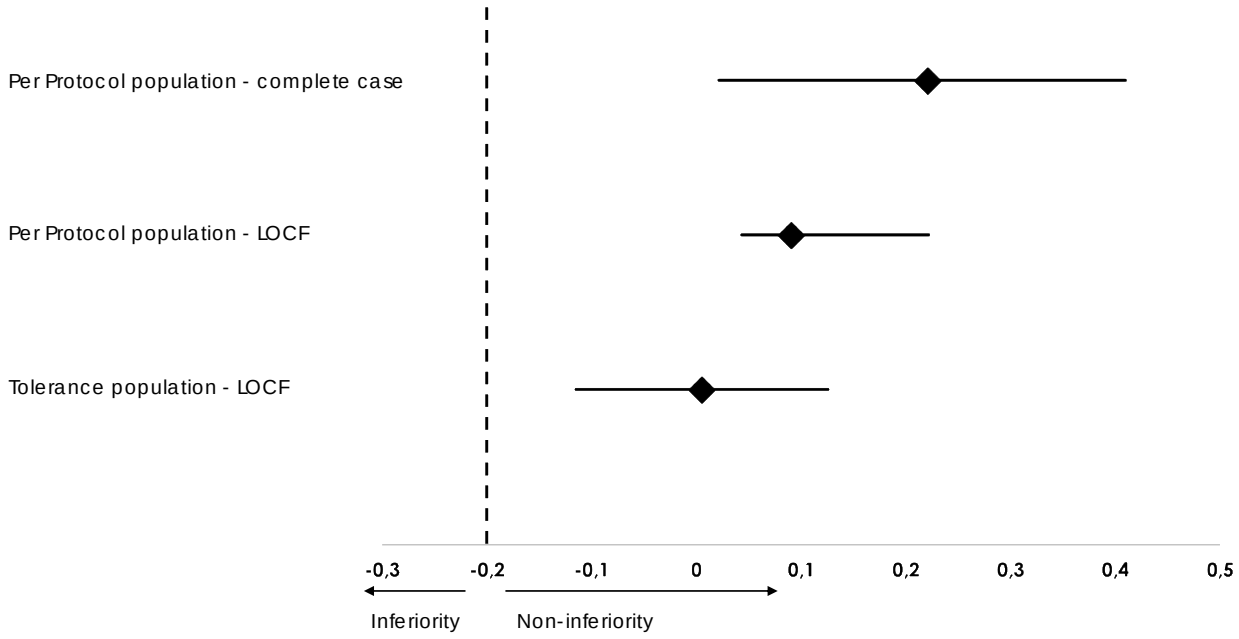

Figure 2. Responder rates difference at 12 months

The difference of responder rate in both group on Per Protocol and Tolerance populations is expressed as mean. The non-inferiority margin on IC90% is set at -0.2 (**dash line**). Lozenges are representing the mean difference between the two treatment groups and segment are representing the IC90%. Whatever the studied population, the difference does not exceed the non-inferiority margin.

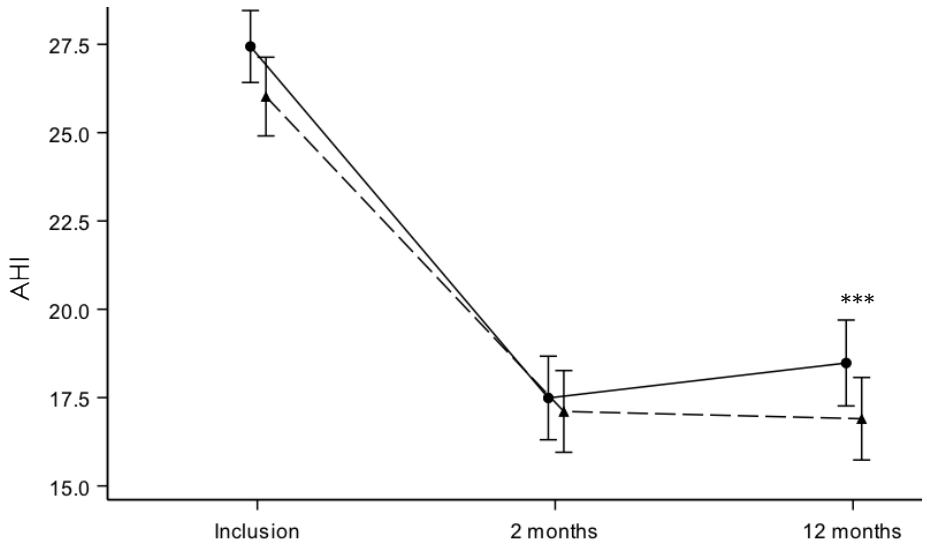

Figure 3. AHI changes from baseline per treatment group (TOL population – LOCF calculation)

Triangles and circles are representing the mean change from baseline over time in ONIRIS® and TALI® groups respectively. Segments are representing the standard error. Significance of evolution from baseline: ***p<0.001 (paired t-test).

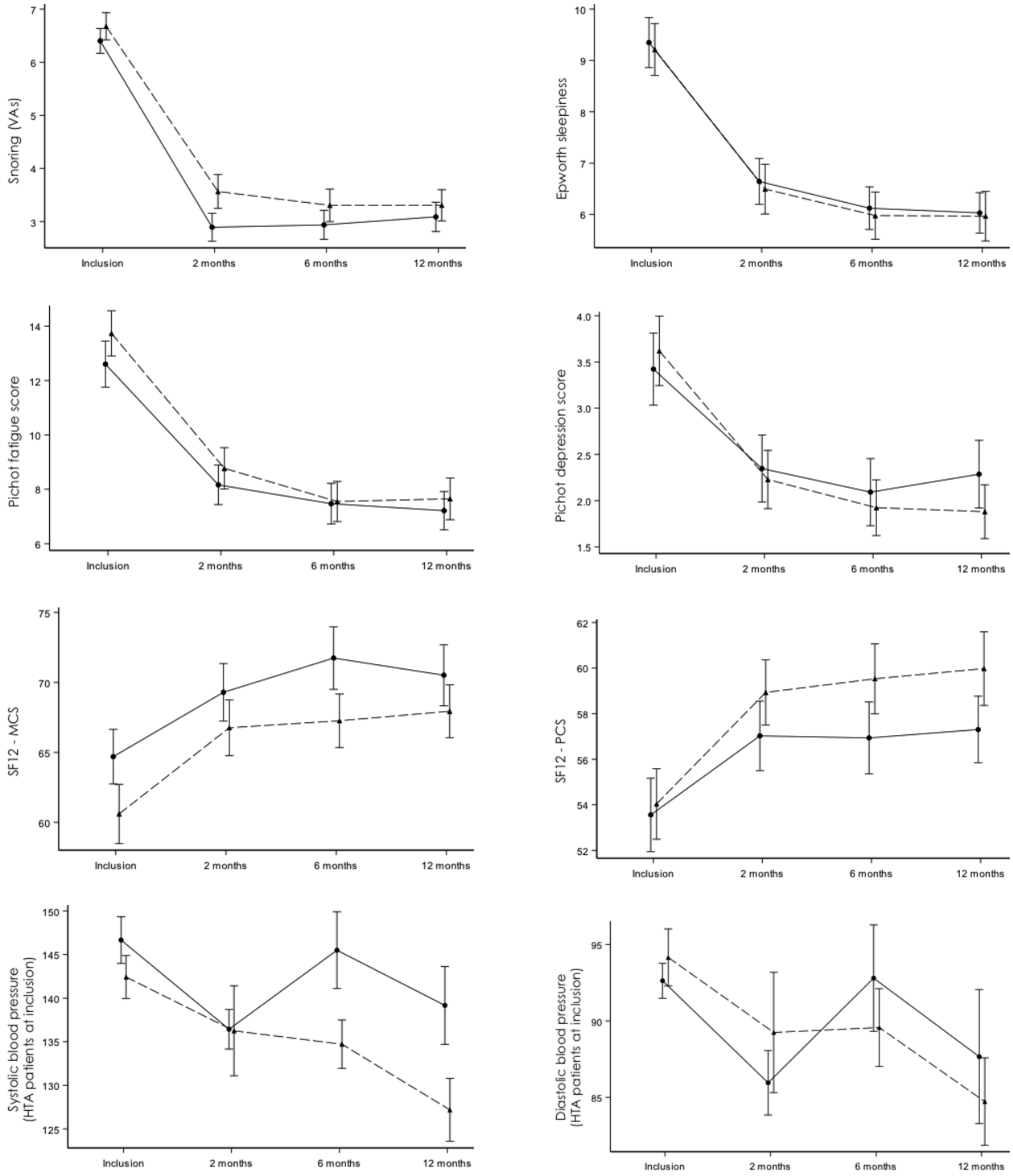

Figure 4. Secondary outcomes changes from baseline per treatment group (TOL population – LOCF calculation)

Triangles and circles are representing the mean change from baseline over time in ONIRIS® and TALI® groups respectively. Segments are representing the standard error.

Table 1. Baseline demographics and clinical characteristics (TOL and PP population)

Characteristic	Population TOL		Population PP	
	TALI (N=98)	ONIRIS (N=92)	TALI® (N=87)	ONIRIS® (N=69)
Age (years)	52.9 (12.3 ; n=98)	49.0 (11.60 ; n=92)	52.9 (12.2 ; n=87)	49.3 (11.2 ; n=69)
Male sex	75 (76.5%)	63 (68.5%)	67 (77%)	50 (72.5%)
Body-mass index (kg/m²)	26.12 (2.80 ; n=98)	25.77 (2.70 ; n=91)	25.91 (2.85 ; n=87)	25.86 (2.71 ; n=68)
MADs indication				
• Refusing CPAP	41 (41.8%)	39 (42.4%)	33 (37.9%)	29 (42%)
• Not tolerating CPAP	57 (58.2%)	52 (56.5%)	54 (62.1%)	39 (56.5%)
AHI.h^{-1}	27.4 (10.1 ; n=98)	26.0 (10.7 ; n=92)	27.1 (9.8 ; n=87)	26.1 (11.1 ; n=69)
Systolic pressure	128.0 (19.5 ; n=97)	126.3 (14.4 ; n=92)	127.6 (19.9 ; n=87)	126.4 (13.7 ; n=69)
Diastolic pressure	81.0 (12.1 ; n=97)	81.3 (11.3 ; n=92)	81.3 (12.3 ; n=87)	81.8 (11.4 ; n=69)
Hypertension (WHO criteria)				
• Mild	20 (20.6%)	21 (22.8%)	18 (20.7%)	15 (21.7%)
• Moderate	7 (7.2%)	5 (5.4%)	6 (6.9%)	4 (5.8%)
• No hypertension	70 (72.2%)	66 (71.7%)	63 (72.4%)	50 (72.5%)
Snoring (10 cm VAS)	6.402 (2.259 ; n=94)	6.675 (2.371 ; n=86)	6.420 (2.203 ; n=84)	6.654 (2.460 ; n=65)
Number of missing tooth	3.9 (3.2 ; n=98)	3.4 (2.4 ; n=92)	3.8 (3.2 ; n=87)	3.4 (2.5 ; n=69)
Partiallly edentulous patient				
• At least one missing tooth	83 (83.9%)	75 (81.2%)	73 (84.7%)	56 (81.5%)
• At least 4 missing teeth	56 (57.1%)	50 (54.4%)	49 (56.3%)	37 (53.6%)

Data are n (%) or mean (SD; number of patients), unless otherwise indicated. TOL = Tolerance population defined as all randomized patients who used the device at least once. PP = Per-protocol population defined as all randomized patients who used the device at least once with no major deviation regarding the established protocol such as non-compliance with major inclusion and exclusion criteria, no assessment of the primary endpoint at 2-month follow-up visit (except for patient reporting a lake of efficacy in between).

Table 2. Responder rates at 12 months per group and analyzed population

Analyzed population	TALI®	ONIRIS®	Difference	IC90%	p-value
PP at 12 Mo	22/38 (57.9%)	24/30 (80%)	0.221	0.0210; 0.4084	0.0015
PP at 12 Mo (LOCF)	40/87 (46%)	38/69 (55.1%)	0.091	0.0426; 0.2221	0.0027
TOL at 12 Mo (LOCF)	40/98 (40.8%)	38/92 (41.3%)	0.005	-0.1151; 0.1248	0.003

Table 3. Evolution of secondary outcomes at 12 months (TOL population - LOCF)

Variable	TALI®	ONIRIS®	p-value
AHI.h^{-1}	-9.0 ± 11.9***	-9.1 ± 9.7***	0.8455 (T)
Snoring (VAS)	-3.4 ± 3.1***	-3.3 ± 3.2***	0.83 54 (T)
Epworth sleepiness	-3.3 ± 3.6***	-3.3 ± 3.9***	0.9563 (T)
Pichot Fatigue	-5.4 ± 7.0***	-6.1 ± 7.5***	0.5085 (T)
Pichot Depression	1.2 ± 3.4**	-1.7 ± 2.9***	0.2882 (T)
SF12 mental score	5.8 ± 19.4**	7.3 ± 17.6***	0.5742 (T)
SF 12 physical score	3.7 ± 14.3*	5.9 ± 13.8***	0.2828 (T)
Diastolic pressure (HTA patients at inclusion)	-5.3 ± 9.0	-9.4 ± 11.5*	0.8455 (T)
Systolic pressure (HTA patients at inclusion)	-14.5 ± 13.5*	-14.3 ± 16.6*	0.0776 (T)

Data are mean ± SD. (T) Student's t test.
Significance of evolution from baseline: *p<0.05; **p<0.01; ***p<0.001 (paired t-test)