Although there is increasing interest in the use of oral appliances to treat obstructive sleep apnea (OSA), the evidence base for this is weak. Furthermore, the precise mechanisms of action are uncertain. We aimed to systematically investigate the efficacy of a novel mandibular advancement splint (MAS) in patients with OSA. The sample consisted of 28 patients with proven OSA. A randomized, controlled three-period (ABB/BAA) crossover study design was used. After an acclimatization period, patients underwent three polysomnographs with either a control oral plate, which did not advance the mandible (A), or MAS (B), 1 wk apart, in either the ABB or BAA sequence. Complete response (CR) was defined as a resolution of symptoms and a reduction in Apnea/Hypopnea Index (AHI) to < 5/h, and partial response (PR) as a 50% reduction in AHI, but remaining 5/h. Twenty-four patients (19 men, 5 women) completed the protocol. Subjective improvements with the MAS were reported by the majority of patients (96%). There were significant improvements in AHI (30 ± 2/h versus 14 ± 2/h, p < 0.0001), MinSaO2 (87 ± 1% versus 91 ± 1%, p < 0.0001), and arousal index (41 ± 2/h versus 27 ± 2/h, p < 0.0001) with MAS, compared with the control. The control plate had no significant effect on AHI and MinSaO2. CR (n = 9) or PR (n = 6) was achieved in 62.5% of patients. The MAS is an effective treatment in some patients with OSA, including those patients with moderate or severe OSA.