Table 2. qADAM Scores during treatment with TNG

Question	V1 score	V4 score	Change from V1–4	p
1: Libido	2.46	3.04	0.58	0.00000132
2: Energy level	2.70	3.41	0.70	0.00000031
3: Strength/endurance	2.85	3.38	0.53	0.00001542
4: Enjoyment of life	3.26	3.57	0.31	0.00534854
5: Happiness level	3.26	3.60	0.35	0.00047582
6: Strength of erections	2.60	3.05	0.44	0.00052518
7: Work performance	3.10	3.58	0.48	0.00010947
8: Fall asleep after dinner	4.12	4.28	0.16	0.14976064
9: Sports ability	2.41	3.03	0.62	0.00000033
10: Height lost	4.37	4.64	0.27	0.04153504

qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; TNG: testosterone nasal gel.

benefit from three times daily dosing, while patients with cumulative scores >8 did not show consistent improvement at the higher dose. Using this rule, 24% of patients would benefit from up-titration, a value similar to the percentage of actual up-titration decisions made during the study based on TT alone and to decisions made by physicians. Thus, these three questions were selected as most likely symptom queries for physicians to examine when consulting patients treated with TNG.

There were no serious treatment-related AEs reported during the conduct of this study. Mean total cholesterol, LDL, HDL, triglycerides, alanine transaminase (ALT), and aspartate aminotransferase (AST) results were all within normal range and mean values observed after dosing were similar to those observed at baseline (visit 1). Table 3 and Fig. 2 show hematocrit levels during the study. There was no significant increase in the hematocrit of TThN patients (mean endpoint hematocrit 42.98%, +0.23% change). TThE (mean endpoint hematocrit 44.92%, -1.27% change) patients experienced a slight but statistically significant (p=0.0052) decrease, however, remained in the normal range.

Table 3. Mean hematocrit values by visit and dose (safety population)

Parameter	All patients	BID	TID
Baseline (visit 1) (mean) (SD, n)	45.36 (5.35, 115)	45.43 (5.58, 85)	45.16 (4.72, 30)
Day 90 (visit 4 BID dose) (mean) (SD, n)	44.43 (3.65, 72)	44.28 (3.43, 44)*	44.67 (4.02, 28)
Day 120 (visit 5 TID dose) (mean) (SD, n)	43.76 (2.44, 22)*	NA	43.76 (2.44, 22)*

*Statistically significant (p<0.05) from visit 1 to visit 4 and from visit 1 to visit 5. BID: twice daily; TID: three times daily; SD: standard deviation.

Discussion

Most topical testosterone preparations have multiple dose levels and require titration.[10] The 2015 *Canadian Medical Association Journal* guidelines for the diagnosis and treatment of hypogonadism[11] state the two key objectives of treatment as: "the improvement in symptoms and the achievement of eugonadal levels of testosterone in the mid-normal range for healthy young men (14–17.5 nmol/L)." These guidelines recognize that higher or lower mid-range serum testosterone concentrations are acceptable when a positive symptom response is observed. When titrating, dose levels are adjusted for safety (dose downward if TT is too high) and efficacy (dose upward if TT is too low). Monitoring TT levels is important because the highest recommended dose of most preparations can produce supraphysiological testosterone levels, which can be unsafe, leading to high levels of hematocrit, which can ultimately require phlebotomy and/or discontinuation.

TNG (4.5% testosterone) is a U.S.- and Canada-approved treatment for hypogonadism that uses a divided dose concept whereby 11 mg are administered either twice or three times daily. The divided dose is efficacious in improving TT levels and symptoms, as discussed here. Furthermore, in an independent arm of the phase 3 program, the three times daily dose was proven safe, with a very low risk of causing supraphysiological TT levels. We have reported additional benefits to divided dosing, including excellent long-term hematology safety and a lessened impact on the hypothalamic-pituitary-gonadal axis (HPG axis), which regulates spermatogenesis and testicular integrity.[12,13] While a divided dose can sometimes lead to issues of compliance, we report in an accompanying analysis that patients found that TNG, when given twice or even three times daily, was superior over topical medication, especially with respect to convenience. Thus, TNG is a unique candidate that might allow titrations to be performed within 90 days based on symptoms, with only a confirmatory TT measurement 30 days after finding the most appropriate dose for treatment. Using symptoms as

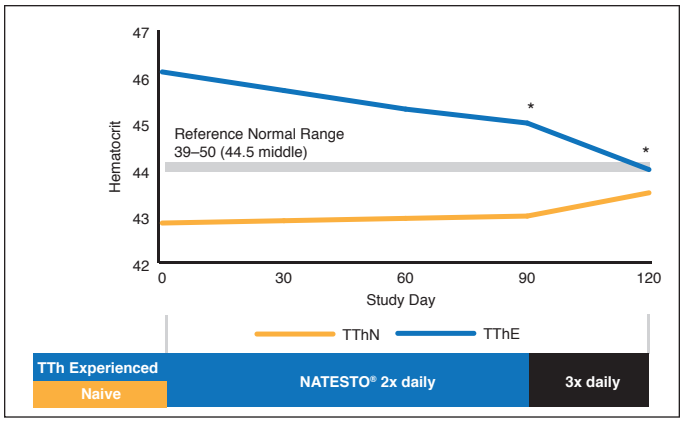

Fig. 2. Changes in hematocrit during study; 47 males on active topical testosterone therapy (TThE) received twice daily dosing. TThE: active topical testosterone therapy; TThN: naive to testosterone therapy.