

Safety and Efficacy of a Non-Invasive 1060 nm Diode Laser for Fat Reduction of the Abdomen

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ABSTRACT

Background: Changes in temperature are known to produce apoptosis in adipocytes. This study examines the use of a non-invasive treatment that applies 1060 nm laser energy transcutaneously to hyperthermically induce disruption of fat cells in the abdomen.

Methods: Thirty-five subjects received application of 1060 nm laser on the abdomen for fat reduction. Ultrasound images and high-resolution two-dimensional photography were recorded at baseline, 6 weeks, and 12 weeks post treatment. Subjects maintained a stable diet and exercise routine throughout the course of the study. Weight was recorded at baseline and each follow-up visit. Three board certified dermatologists were trained as blinded evaluators and tasked with identifying before and after photographs from randomized, paired baseline, and 12-week photographs. Ultrasound images were used to measure the fat thickness change from baseline at 6 and 12 weeks. Level of patient satisfaction was graded at 12 weeks using a 6 point Likert scale.

Results: 23% of subjects were Fitzpatrick IV-VI. Blinded evaluators correctly identified the post-treatment photograph 95% of the time (88%, 97%, and 100%). Mean reduction in fat layer thickness from baseline was statistically significant ($P<0.001$) at both 6 weeks (1.5 +/-1.23 mm) and 12 weeks (2.65 +/-1.41 mm). Mean weight change was +0.1 lb. Side effects were mild to moderate including edema, tenderness, and induration mostly resolving within 1-3 weeks post treatment. No serious adverse events were reported.

Conclusion: 1060 nm based laser treatment can consistently reduce the fat contour in the abdomen with an excellent safety profile in all skin types. The study met all three of its prospectively defined endpoints of success.

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INTRODUCTION

Body contouring with liposuction is consistently one of the two most popular aesthetic surgical procedures.[1] More recently, a number of options for non-invasive body contouring have become available. These have been even more popular and show a double-digit growth of 18.7% in 2015 compared to the prior year.[1] This demand is fueled by the growing desire to avoid invasive procedures where possible.

Some non-invasive fat reduction options create immediate necrosis of adipocytes due to tissue coagulation.[2] Others achieve a similar endpoint with cavitation.[3] An alternative strategy creates adipocyte damage that is sub-lethal, resulting in apoptosis over time. This endpoint can be produced using tissue heating or tissue cooling. Laboratory studies have demonstrated the ability to produce apoptosis in a high percentage of the adipocyte population heating to temperatures of 42-47 C for a period of 15 minutes.[4] A variety of energy sources can potentially be used to produce such heating. Preliminary laboratory and clinical studies demonstrated the ability to damage adipocytes using a 1060 nm diode laser device to target this endpoint.[4,5]

This study reports the experience of using a non-invasive 1060 nm diode laser device in the pivotal clinical trial for safety and efficacy of fat layer reduction in the abdomen that has since been approved by FDA for this indication.

PATIENTS AND METHODS

Study Device

The device used in this study provided 1060 nm diode laser light exposure through a 4X6 cm optical window that was simultaneously cooled with circulating fluid to 15°C (Cynosure, Westford, MA). The treatment head was held in contact with the skin overlying the targeted fat using straps passed around the subject's waist. Energy densities ranging from 0.9-1.4 W/cm^2 were used.

Study Design

A prospective controlled study was conducted at two centers, with each enrolled patient receiving a single non-invasive treatment. Institutional review board approval of the protocol was obtained and patients signed an informed consent form.

This study included subjects who had to be healthy males or females between 20 and 65 years of age with a BMI of 32 or under and with unwanted fat in the abdominal region. Subjects were excluded for a variety of conditions including skin hypersentivities, anti-coagulant, or anti-platelet therapies, previous surgery, or liposuction in the treatment area, pregnancy, or a history of

keloids, among others. Subjects were instructed to maintain a stable diet and exercise routine throughout the study. Weight was recorded at all visits. Photographs were taken in a studio at each site with fixed positioning for the camera, lights, and subject, as well as fixed manual exposures.

Treatment area was determined by the investigator in all subjects based on the area of greatest need for contour reduction, which was then marked with a template (Figure 1). Similar templates were used to identify and mark the area for ultrasound imaging, which were retained for accurate identification of the correct location for imaging at subsequent visits. A Sonosite Micromaxx ultrasound system was used with a HFL38-13-6 MHz transducer. The same technician performed the ultrasound and used a validated technique to assure consistency. This included identification and matching of template position, matching of subcutaneous connective tissue architecture, and pressure/ultrasound gel thickness during imaging.

A single treatment session was performed for all subjects. The laser head was applied to adjacent areas within the marked treatment area for a single exposure until the entire marked area was treated. Exposure time was 25 minutes. Patient discomfort was assessed periodically during the treatment using a graded scale (0=none -10=worst) and energy density was adjusted to maintain a score of 3-4 (Table 1). Aftercare included cool compresses or acetaminophen if needed.

Patients returned for follow up at 6 and 12 weeks where photography and ultrasound were repeated. A visit took place at 1 week (n=30) to assess the incidence of early post-treatment adverse events and to record the ultrasound appearance of exposed fat during early healing. At 12 weeks, subjects graded their satisfaction with the results using a 6-point balanced Likert scale (1=extremely satisfied, 2=satisfied, 3=slightly satisfied, 4= slightly dissatisfied, 5=dissatisfied, 6= extremely dissatisfied).

Assessments and Endpoints

Photographs were evaluated in randomized pairs of baseline and 12 week photographs for each subject. Three blinded reviewers, who were board certified dermatologists with previous study experience in non-invasive body contouring, attended a training session prior to grading. The evaluators were tasked with correctly identifying the pre- and post-treatment photograph in each pair. The primary endpoint of the study was considered a success if they made a correct identification in 80% of the pairs. A secondary endpoint was demonstrating a statistically significant difference in fat layer thickness between baseline and 6 and 12-week follow-up visits (paired T-test, $P<0.05$). The final endpoint was subject satisfaction of 80% or greater.

TABLE 1.

Treatment Pain Scale
Universal Pain Scale:

TABLE 2.

Demographics	All (N=35)		Bass (N=18)		Doherty (N=17)	
Age						
Average (years)	47.6±9.4*		47.0±12.0		48.8±6.3	
Range	23-61		23-61		34-59	
BMI						
Average	25.5±2.6		25.7±2.7		25.2±2.5	
Range	20.9–31.6		20.9–31.6			
Sex	No.	%	No.	%	No.	%
Male	2	6	2	11	0	0
Female	33	94	16	89	17	100
Racial Demographics						
Caucasian	29	83	14	78	15	88
African American	2	6	2	11	0	0
Hispanic	3	9	2	11	1	6
Asian	1	3	0	0	1	6
Fitzpatrick Skin Type						
I	0	0	0	0	0	0
II	14	40	11	61	3	18
III	13	37	2	11	11	65
IV	6	17	3	17	3	18
V	0	0	0	0	0	0
VI	2	6	2	11	0	0

*Avg±S.D=Average percent±standard deviation

FIGURE 1. (A) Selection of treatment head positioning to address observed contours. (B) Treatment areas marked.

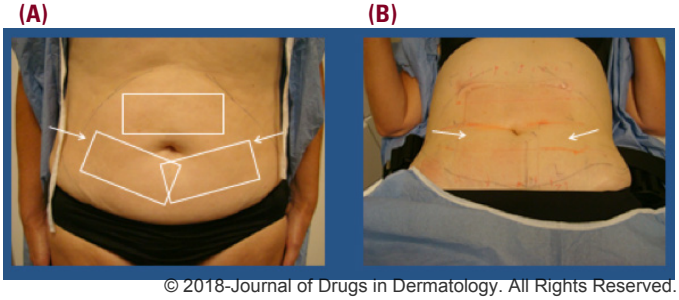


TABLE 3.

Enrollment Summary at 2 Study Centers	
Enrollment Status	**No. subjects**
Enrolled and received treatment	35
Discontinued due to an adverse event	0
Withdrew, were lost-to-follow-up or discontinued (not due to adverse event)	1
Ongoing Subjects	0
Completed the Study	34

TABLE 4.

Subject's Recorded Weight and Change Throughout the Study		
	Weight	**Change from Baseline**
Baseline	149.1±21.8* (111–196)	—
Week 6	150.5±22.3 (112–201)	1.4±2.5 (-5–5.7)
Week 12	149.2±21.6 (112.4–196)	0.1±2.7 (-5.2–5.6)

Avg±S.D. (Min–Max)=Average weight±Standard Deviation (Minimum and Maximum weight)

RESULTS

The two study centers enrolled 35 subjects (18 at Site 1 and 17 at Site 2). The majority of subjects treated were Caucasian (83%). Fitzpatrick skin types II-III were 77% and type IV-VI were 23% of subjects with no Fitzpatrick I subjects enrolled. 2 (6%) males and 33 (94%) females were treated with an average age of 47.6 +/-9.4 years (range, 23-61) and average baseline BMI of 25.5+/-2.6 (Table 2). Pre-treatment evaluations for enrolled subject recorded average weight at 149.1 (+/- 21.8 pounds, with BMI ranging from 22 to 31, and fat thickness layer in the proposed treated area ranged from 0.61cm to 2.95cm.

Of the 35 subjects, none were discontinued due to an adverse event. 34 subjects completed the study with one lost to follow up. Enrollment data is included for all 35 subjects (Table 3).

Efficacy

The efficacy analysis included 34 subjects based on the availability of complete 12-week photographs and ultrasound images. One additional subject was excluded due to a mismatch in the anatomic site of the ultrasound images from baseline and 12 weeks.

Subjects' weights varied modestly over the course of the study. At 6 weeks, the average change in weight was 1.4+/- 2.5 lbs., diminishing to only 0.1+2.7 lbs. at 12 weeks. The greatest weight changes were little more than 5 lbs. either up or down (Table 4). At the 6-week follow-up visit, average weight was 150.5 (+/- 22.3) and at 12 weeks 149.2 (+/-21.6) pounds for an average weight change of 0.1 pounds.

Blinded evaluators correctly identified pre- and post-photographs on average 95% of the time as a group (88%, 97% and 100%, individually).

Figures 2-4 illustrate three representative subjects who uniformly show a flattening of abdominal contour in the treated areas regardless of weight gain or loss.

Ultrasound images showed a reduction in fat layer thickness from baseline of 1.5+/-1.23 mm at 6 weeks and 2.65+/- 1.41 mm at 12 weeks. The reductions at both 6 and 12 weeks were statistically significant compared to baseline based on a paired t-test (P<0.001; Table 5).

At 12 weeks, 91% (31/34) of subjects were satisfied (slightly satisfied, satisfied, or extremely satisfied) with 85% being satisfied or extremely satisfied (Table 6).

Adverse Events

There were no deaths, serious adverse events (SAE's), or unanticipated device-related events reported in this study. All the adverse events were typical laser treatment reactions and were self-limited without treatment (see Table 76). Discomfort during treatment was graded at 3.7+1.3 (n=35). This was similar between the two study centers, 3.7±1.4 (n=18) and 3.8±1.2 (n=17). Post-treatment tenderness was the most common adverse event. 74% of adverse events were reported as mild,

TABLE 5.

Fat Reduction: Mean Thickness Reduction of Adipose Layer Compared to Baseline						
	All (N=33)		**Site 1 (N=17)**		**Site 2 (N=16)**	
Week Post-Treatment	**Subject Reduction (%)**	**Thickness Reduction (mm)**	**Subject Reduction (%)**	**Thickness Reduction (mm)**	**Subject Reduction (%)**	**Thickness Reduction (mm)**
6	6.5±5.0*	1.50±1.23	6.8±5.8	1.60±1.56	6.3±4.0	1.40±0.77
12	11.5±6.3	2.65±1.41	10.6±6.0	2.46±1.50	12.5±6.6	2.85±1.34

*Avg±S.=Average percent±Standard Deviation

TABLE 6.

Subject Satisfaction							
	Score	All		Site 1		Site 2	
		(N=34)	%	(N=17)	%	(N=17)	%
Extremely Satisfied	1	10	29	3	18%	7	41%
Satisfied	2	19	56	10	59%	9	53%
Slightly Satisfied	3	2	6	2	12%	0	0%
Slightly Dissatisfied	4	2	6	1	6%	1	6%
Dissatisfied	5	1	3	1	6%	0	0%
Extremely Dissatisfied	6	0	0	0	0%	0	0%

26% moderate, and none as severe. Mild reported events in the individual studies were; Site 1 (17/19, 89%) and at Site 2 (14/23, 61%). For the entire study, 26% of events were reported as moderate. Moderate reported events in the individual studies were; Site 1 (2/19, 11%) and at Site 2 (9/23, 39%). No events were reported as severe.

There was one instance of erythema that resolved within a day. Mild tenderness (n=26) and edema (n=3) were commonly seen, resolving with 4-7 days. Occasional ecchymosis (n=2) was mild and resolved within 12 days. Occasional palpable firmness (n=10) resolved within 55 to 69 days except in one case (present at 3-month follow-up visit as a subtle finding on careful exam and absent at 6 month follow-up visit). There were no reports of blistering, pinpoint bleeding, crusting, scabbing, itching, pustules, skin burns, scarring, infection, allergic reaction, hypopigmentation, and hyperpigmentation.

DISCUSSION

Hypothermic and hyperthermic-induced adipocyte injury elicits an inflammatory response. Human and animal histological findings indicate that precisely applied thermal injury triggers apoptosis of the adipocytes, inducing an inflammatory response resulting in mobilization of macrophages.[4,7] The injured and dead adipocytes are engulfed and digested by macrophages, and in the ensuing weeks to months the injured adipocytes are removed through the inflammatory process.[8-10] Much of the evidence for the thermally induced inflammatory response comes from studies of cryolipolysis where reduction in subcutaneous fat is accomplished without injury to adjacent tissues, and the induced inflammatory response has no effect on serum lipid profiles or liver tests.[11] A hypothermic action *decreases* subcutaneous tissue temperature below body temperature and maintains it for prolonged period of time (tens of minutes).[12] The amount of temperature decrease to achieve efficacy is greater than 30°C

Hyperthermic treatment *increases* adipose tissue temperature to 42-47°C for sustained time, also resulting in adipocyte injury and eliciting an inflammatory response.[4] The amount of temperature increase to achieve this target temperature is less than 10°C. The amount of tissue damage can be quantified from the relationship between exposure time and tissue temperature.[13] At moderate increase in temperature to 6°C above normal (ie, 43°C), the structural integrity of the lipid bilayer is lost and at 45°C for more than 5 minutes cell membranes show damage.[4,14,15] The injured adipocytes are removed through body inflammatory processes.[4-6]

Previous studies with this 1060 nm diode laser prototype established the ability of prolonged exposure of subcutaneous tissue

FIGURE 2. (A) Three quarter view pre-treatment. (B) Three quarter view 12 weeks post-treatment. (C) Anterior view pre-treatment. (D) Anterior view 12 weeks post-treatment. Note flattening of infra-umbilical fullness. Weight change: +1 lb.

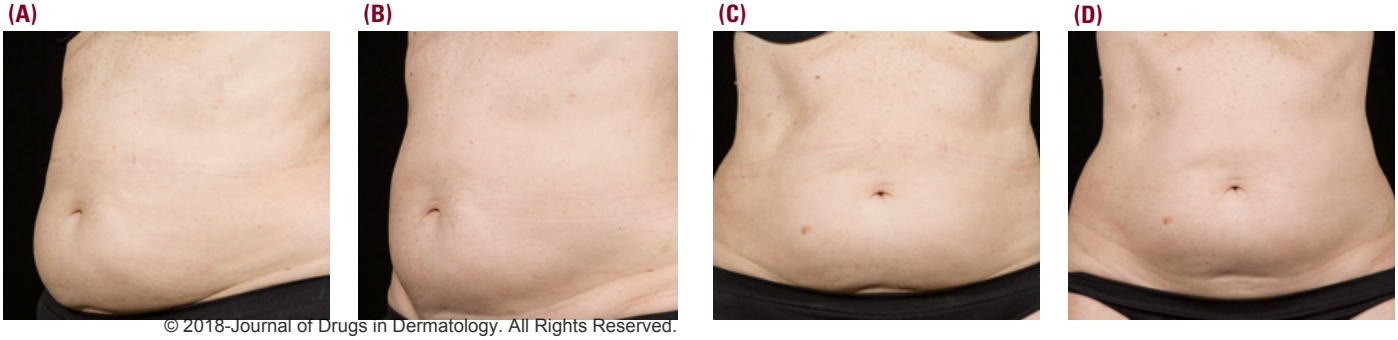
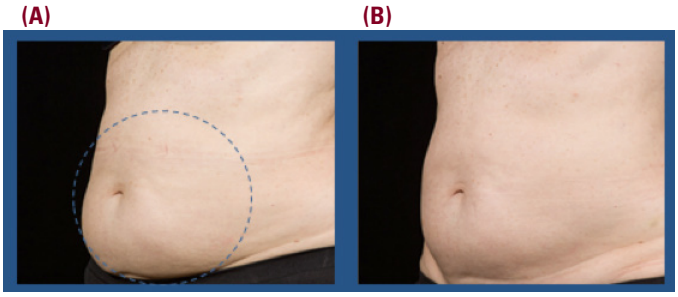


FIGURE 3. (A) Pre-treatment with exposed area outlined. (B) 12 weeks post-treatment. Weight change: +1 lb.

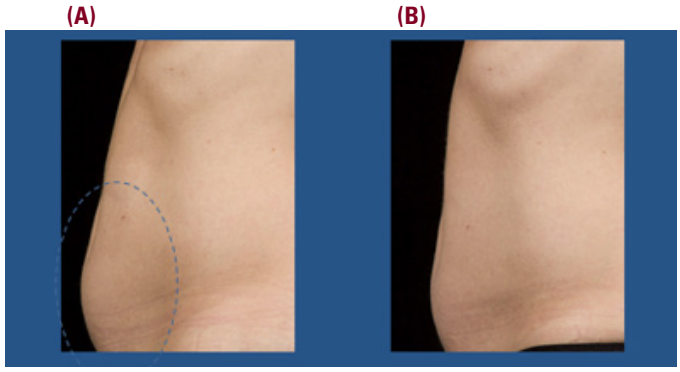


at the hyperthermic temperature range 42°C to 47°C to cause adipocyte injury and induce inflammatory response to remove damaged adipocytes over the ensuing months.[5] Optimal treatment time was between 20-25 minutes. Treatment times longer than 30 minutes were associated with a risk of developing palpable nodules in subcutaneous fat. Treatment times less than 20 minutes had minimal effect.[4]

Radiation at 1060 nm wavelength heats the fat layer with controlled temperature elevation, distributing the heating more evenly over a broad zone conspired to higher wavelengths.[16,17] Studies of hyperthermia induced tissue damage and ex vivo temperature measurements have shown that hyperthermic temperature can be achieved and maintained in subcutaneous adipose tissue by a 1060 nm laser in conjunction with surface cooling.[14-16] The 1060 nm optical energy does not have a specific chromophore in the skin and therefore generates non-specific heating.

Other treatments that depend on heat destruction of adipose tissue are ultrasound[18] and radiofrequency.[4] With high intensity focused ultrasound (HIFU) the temperature quickly reaches 56°C, and has been reported to rapidly raise tissue temperature over 70°C,[19] which is effective in coagulative necrosis of the adipocytes and subsequent reduction of the fat layer. Therefore,

FIGURE 4. (A) Pre-treatment with exposed area outlined. (B) 12 weeks post-treatment. Weight change: +1.8 lb.



HIFU has the potential to cause nonselective instantaneous cell necrosis at the designated target.[19,20] Radiofrequency technology utilizes the resistance (impedance) of the tissue itself to generate heat rather than directly transferring heat. Because adipocytes have high tissue resistance and low heat transfer coefficients, they generate significant heat when radiofrequency energy is passed through the tissue and at the same time limiting the spread of this heat to surrounding structures.[21]

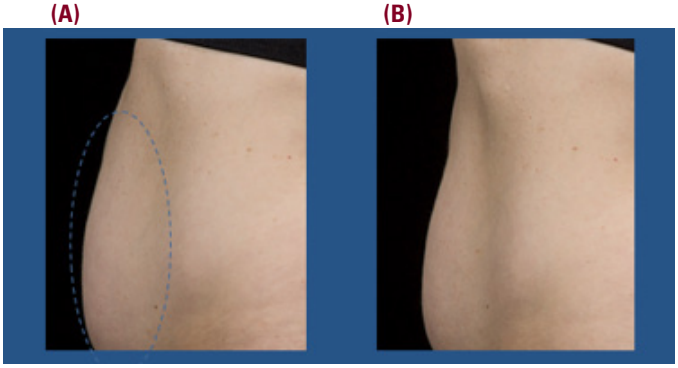
Another treatment, cryolipolysis, depends on cold-induced adipocyte apoptosis. This treatment is based upon the greater susceptibility of lipid-rich adipocytes to cold injury compared to surrounding water rich cells. The phenomenon was established in a study on pigs that showed damage to subcutaneous fat without damage to the overlying skin.[9,22] A prior study compared cryolipolysis to the 1060 nm diode laser for fat reduction. Based on ultrasound, MRI, and photographic evaluations the use of the 1060 nm laser treatment gives comparable results to cryolipolysis.[5]

Empirical results with patient discomfort score correlate with the target temperatures of the treatment. Most patients will perceive temperatures in the low 40 C range to be warm but

TABLE 7.

Adverse Events at 2 Study Centers: N = 35 Subjects								
Event	No. of Subjects with AE	% Subjects	No. of Subjects			Duration (days)		
			Mild	Moderate	Severe	Average	Min	Max
Pain	26	74%	18	8	0	7.4	0	28
Edema	3	9%	3	0	0	4.3	3	7
Erythema	1	3%	1	0	0	1	1	1
Nodule	8	23%	5	3	0	70	35	139
Hardness	2	6%	2	0	0	55	33	77
Bruising	2	6%	2	0	0	12.5	7	18
Total No. AE			31	11	0			
% AE			74%	26%	0%			

FIGURE 5. (A) Pre-treatment with exposed area outlined. (B) 12 weeks post-treatment. Weight change: -4.4 lb.



temperatures above 45 C to be uncomfortably hot. After the initial heat build phase, treatment fluence is adjusted to the point of discomfort in the range of 3-4/10 on a pain scale. This range-finding places the tissue temperature in the therapeutic range. A patient reporting a discomfort score of 5 out of 10 may experience pain or overheating. A patient who reports a discomfort score of 1 or 2 may not realize the maximum potential results. Thus, it is no accident that the treatment was not reported as painful by the patients since the fluences were tailored to achieve that result. The contour reductions presented here were produced at these comfortable fluences.

The contour reductions showed no sharp transition at the edge areas of the treatment. Given the application method, applicators attached via a belt and frame system, both light scattering and heat feathering are likely at play here. Tapering of the temperature gradient and therefore the fat reduction effect at or beyond the edge of the applicator would be expected and matches clinical observations in this study.

The use of a light-based and heat-based method raises several concerns and possibilities. The potential for thermal effects from melanin absorption in the skin are potentially concerning. Multiple Fitzpatrick VI patients were treated with no blisters or other skin effects observed. The thermodynamic problem of competing contact cooling of the skin and deeper heating of subcutaneous fat was solved in this experimental device producing fat layer reduction without skin adverse events. Heat produces various effects that cold exposure may not produce or produce in equal measure including release of heat shock proteins, among other effects. The potential to allow some heating of the skin with a small modification of parameters exists. Even with the existing exposure, fibrous septae running between the skin and fascia are within the heated zone and likely to show some response to the hyperthermic exposure during healing.

Exposure time in this study was 25 minutes. This allows treatment in significantly less time than antecedent devices. Since many patients desire to treat more than a single small bulge, the time savings, multiplied over several or many treatment cycles, becomes substantial. One of the principal patient motivations in selecting a non-surgical option is ease, convenience and no need to disrupt the normal life schedule. Time savings is a premium issue in this context that cannot be overstated.

CONCLUSION

The current study is a prospective, controlled (treatment versus no-treatment) study to evaluate a non-invasive 1060 nm diode laser with contact cooling intended for non-invasive treatment of the abdomen to achieve disruption and removal of adipocytes for contour reduction. In conjunction with the study of flank treatment with the same device (Katz 2015), this formed the pivotal study data for FDA approval that has since been granted.

The data showed the 1060 nm laser hyperthermic treatment produced a consistent, observable reduction in abdominal contour compared to baseline based on ultrasound measurements and grading by blinded evaluators. Subjects are highly satisfied with the treatment, which is safe with only mild and transient side effects. No serious adverse events or unanticipated adverse device events were encountered. Treatment time is reduced compared to currently available alternative technologies with an easily tolerable treatment discomfort profile comparable to alternatives and minimal if any recovery discomfort.

DISCLOSURES

Both authors served as consultants for the study sponsor as well as serving on the speakers bureau. Dr. Doherty serves as medical director for the study sponsor.

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