

# Analysis of the Safety and Reliability of a Hydrothermal Ablation System

## A Multicenter, Prospective Postmarket Study

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**OBJECTIVE:** To obtain information on practitioner experience in the use of the Genesys HydroThermAblator (HTA) System under normal clinical conditions through documentation of the system's acute safety features, in terms of burn rates, and its technical reliability.

**STUDY DESIGN:** This was a prospective, observational, multicenter, postmarket interventional clinical trial with outcome measures of acute (within 21 days post-procedure) safety, serious adverse device effects, and technical malfunctions in a population of premenopausal women  $\geq 18$  years of age.

**RESULTS:** A total of 992 women (mean age,  $41.7 \pm 6.8$  years; range, 22–65 years) were enrolled in 18 clinical sites throughout the United States. The Genesys HTA System provided low burn rates in the intent-to-treat ( $n = 992$  [0.4%] [95% CI 0.1–1.0%]) and evaluable ( $n = 931$  [0.2%] [95% CI 0.1–0.8%]) subject populations. Only 1 burn was clinically significant and was defined as a serious adverse device effect (1/992 [0.10%

[95% CI 0.0–0.6%]). Fifty-three (5.1%) technical malfunctions occurred in 44 procedures, and 27 (27/44 [61.4%]) patients completed their procedures after 31

(31/ 53 [58.5%]) technical problems were addressed and resolved.

**CONCLUSION:** The Genesys HTA System delivers a safe and reliable treatment option for premenopausal women with heavy menstrual bleeding. (J Reprod Med 2014;59:299–

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**The rate of patient burns ... was low, and the clinically significant burn rate was considerably less than the 0.42% projected by the FDA.**

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**Keywords:** endometrial ablation, Genesys HydroThermAblator System, gynecologic surgery, heavy menstrual bleeding, hydrothermal ablation, hydrothermal ablation complications, hysteroscopy.

Heavy menstrual bleeding can significantly affect the physical, emotional, and psychosexual well-being of premenopausal women, with resultant decrease in quality of life and productivity and

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Oral presentation at the American Association of Gynecologic Laparoscopists 42nd Global Congress on Minimally Invasive Gynecology, Washington, D.C., November 10–14, 2013.

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**Financial Disclosure:** All authors received research support from the study sponsor (Boston Scientific, Natick, Massachusetts). Dr. Berman is a consultant for and participates in the sponsor's Speaker's Bureau. Dr. Livingston receives support from the study sponsor for lectures and the development of presentations. The study sponsor provided independent third-party assistance with the development of the manuscript (Wainwright Medical Communications, Los Gatos, California).

increase in direct and indirect healthcare costs.<sup>1-5</sup> Of the approximately 600,000 hysterectomies performed annually in the U.S., 25–30% are for the management of heavy menstrual bleeding.<sup>6</sup> Medical and minimally invasive uterine-preserving surgical treatment options have been developed to minimize the morbidity associated with hysterectomy, and second-generation endometrial ablation (EA) procedures have provided conservative, outpatient alternatives. Immediate outcomes of EA therapies have addressed the safety of the patient and of the operator/surgeon. However, each second-generation nonresectoscopic EA study has been linked to potential risks to the patient, such as uterine perforation and thermal injuries to the bowel, vulva, perineum and buttocks depending on the technique and nature of the ablative method.<sup>7-9</sup>

The current generation of hydrothermal ablation systems (Genesys HydroThermAblator [HTA] System, Boston Scientific Corp., Natick, Massachusetts) was approved for clinical use in 2010 with an improved design to deliver the same therapeutic benefits as the earlier HTA system,<sup>10</sup> improve operator performance, and impart new safety features for the benefit of the patient and device operator. The purpose of this U.S. Food and Drug Administration (FDA)–mandated observational registry was to obtain clinical experience on the use of the Genesys HTA System under normal clinical conditions and to document its acute safety features and technical reliability. The primary objective was to determine the rate of clinically significant burns—deep, second-degree burns that involved both internal and external anatomy or that required medical or surgical intervention and full-thickness third-degree burns. Non-clinically significant burns were those that were not clinically significant through 21 days of follow-up. The latter included first-degree burns and superficial second-degree burns not involving both internal and external anatomy and not requiring medical or surgical intervention. Secondary objectives of this study were the assessment of operator-reported technical complaints and device reliability and serious adverse device effects.

### Materials and Methods

This study was designed as a prospective, observational, multicenter, postmarket interventional clinical trial with outcome measures of acute (within 21 days postprocedure) safety, serious adverse device effects, and technical malfunctions. Recruitment of

premenopausal women  $\geq 18$  years of age began in November 2010, with enrollment of the last patient in June 2012. All subjects provided informed consent and were enrolled at 2 university medical centers and 16 private practices and surgery centers throughout the continental U.S.

All sites obtained local or central institutional review board approval of the protocol. The study (ClinicalTrials.gov Identifier: NCT01197547) was conducted in accordance with the general ethical principles detailed in the Declaration of Helsinki and was in conformance with applicable guidelines for Good Clinical Practices, the U.S. Code of Federal Regulations for conducting clinical studies, and other applicable local regulations related to the rights and welfare of human subjects who participate in medical research, whichever provided the greater protection of the participants.

Potential participants were self-referred or were referred by their healthcare providers. Study eligibility requirements are presented in Figure 1. The study follow-up period was  $\geq 21$  days, depending on evidence of any thermal burns.

The current and newly designed Genesys HTA System is software-controlled and comprises an operational unit (the control unit, pedestal, and intravenous pole), which interfaces with a procedure set (a 7.9-mm sheath, cassette, and drainage bag). Also incorporated on the original HTA System procedure sheath, the Genesys System procedure sheath includes a “cervical seal assist,” which is a finned silicone tube at the distal end of the sheath

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#### Inclusion criteria

Premenopausal women  $\geq 18$  years old with excessive uterine bleeding due to benign causes  
Childbearing is complete

#### Exclusion criteria

Pregnant or desiring pregnancy in the future  
Known or suspected endometrial carcinoma or premalignant change of the endometrium, such as adenomatous hyperplasia  
Active pelvic inflammatory disease or pyosalpinx  
Hydrosalpinx  
Patulous cervix such that a tight cervical seal cannot be established and maintained around the procedure sheath  
Anatomic condition (history of previous classical cesarean section or transmural myomectomy) or pathologic condition (long-term medical therapy) that could lead to myometrial weakening  
Presence of an intrauterine device  
Active genital or urinary tract infection

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**Figure 1** Inclusion and exclusion criteria.

used to gain and maintain a tight seal between the distal portion of the device and the endocervical canal, thereby minimizing the risk of leaks (Figure 2A). Once the physician positions the finned sheath, s/he engages the tenaculum stabilizer (Figure 2B). This allows the tenaculum and sheath to perform as a single unit that can be held in one hand while safe positioning is maintained.

For the cases included in this report, the following procedures were used. During setup the operator inserted a standard ( $\leq 2.9$ -mm) hysteroscope via a reusable adapter into the disposable sheath for preoperative and intraoperative visualization. Each physician dilated the cervix only if needed and then performed diagnostic hysteroscopy with sterile, room-temperature saline while testing the seal integrity of the sheath within the uterine cavity. Once the system's seal integrity check was executed and the seal confirmed, the physician began the ablation procedure. Multiple device sensors controlled and monitored heating of the saline to and cooling from

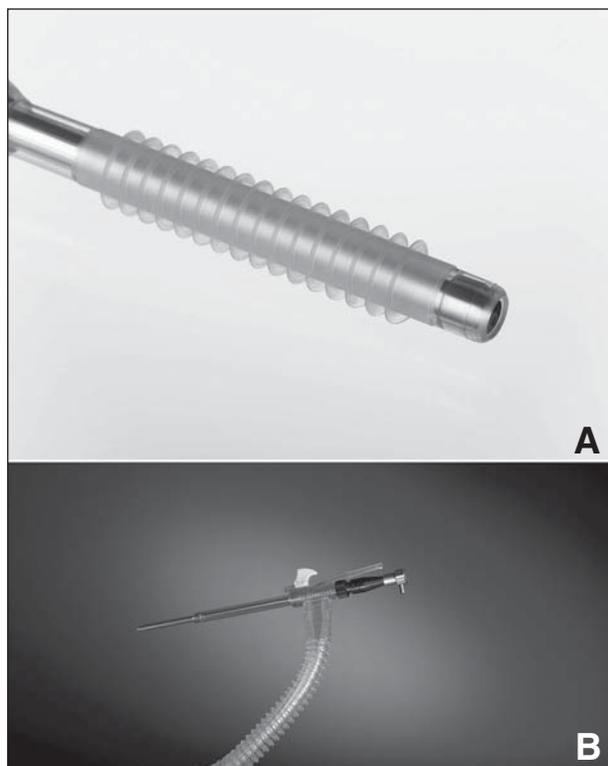
90°C as well as cycle time, continuous seal integrity, saline flow, and perfusion pressure. Upon completion of the procedure, the physician assessed the patient for potential internal or external burns that might have been caused by a cervical leak. The physician categorized any burn as clinically or not clinically significant and followed the patient to 3 weeks postprocedure and beyond, if necessary. Physicians well experienced with hysteroscopic procedures were selected to participate in the registry. The level of physician experience with the HTA system varied in this registry study so as to provide a normal curve of clinician familiarity with the device and procedure.

Data were collected for each patient on the day of her procedure, and all procedures were performed per the Directions for Use and standard of care. Procedure date, burns, serious adverse device effects, technical complaints, and any interventions were recorded and reported by the physicians. Data on all used procedure sets were captured. Procedures in which a tight cervical seal could not be established or maintained were canceled.

#### Statistical Analysis

The historical burn rate of deep second and third degree burns for the HTA system prior to the release of the ProCerva sheath was 0.32%, as determined by a passive (user) reporting system. Also, under the passive system, the rate of burns following the release of the ProCerva Sheath was 0.14%. The impact of a proactive collection process, such as with a subject registry, on the burn rate estimate was unknown. The company worked with the U.S. FDA to establish a hypothesis that the proactive collection would increase the rate estimate by a factor of 3. Therefore, under a proactive system, it was assumed that the rate of clinically significant patient burns would not have been more than 0.96% (~1.00%) prior to the ProCerva sheath and 0.42% after the release of the new sheath. The total number of enrolled subjects was based on an exact one-sided test for one binomial population (independent patients within and across centers) at a significance level of 0.05, a power of 0.998, and an assumed attrition rate of 10%; thus, at inception of the study 1,458 enrolled subjects were required for final analysis.

Subsequently, a series of subject enrollment stopping rules were approved by the FDA and incorporated into the protocol. If the null hypothesis could be rejected and the primary endpoint could be



**Figure 2** (A) Distal tip of 7.9-mm Genesys HTA sheath with ProCerva finned silicon sheath. (B) The 7.9-mm Genesys HTA sheath with tenaculum stabilizer in place. (Photographs courtesy of Boston Scientific, Natick, Massachusetts.)

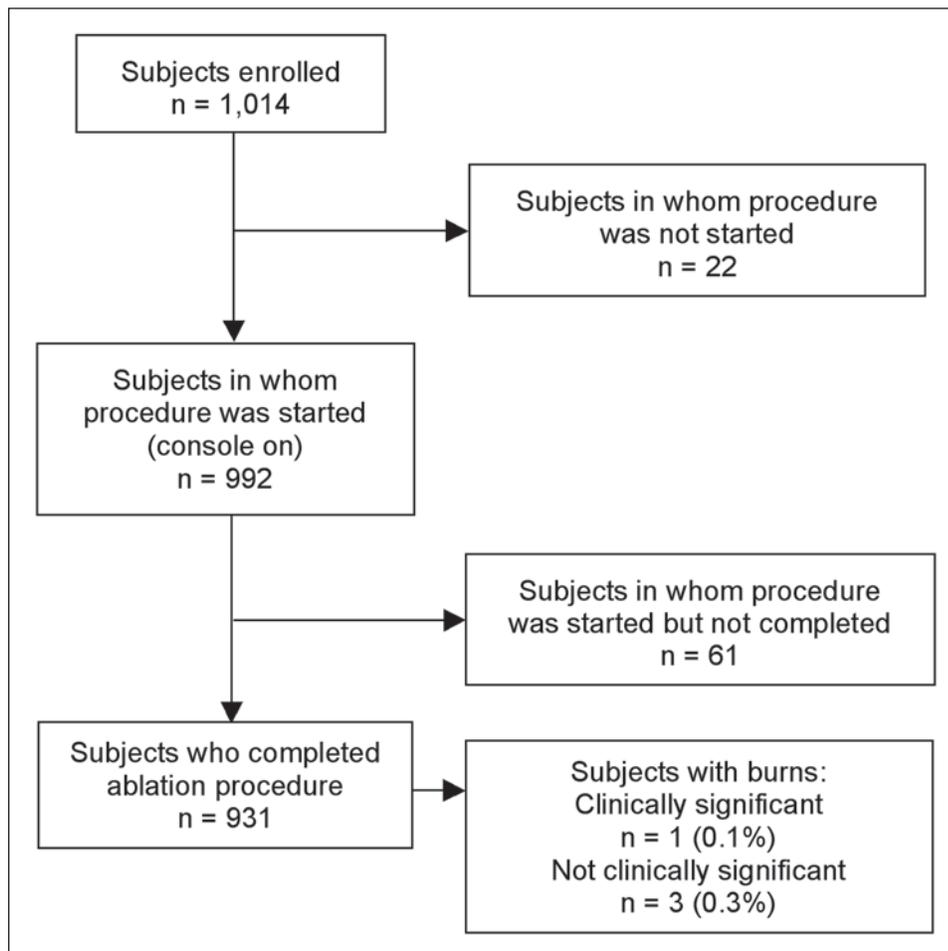
achieved with a smaller sample size, then the study enrollment would be halted. The stopping rule was met with 984 evaluable subjects ( $p < 0.01$ ) to reject the null hypothesis if  $p \leq 0.0198$ . The applied statistical test was an asymptotic one-sided binomial test of superiority at each interim analysis of a group-sequential design using an O'Brien-Fleming stopping rule.<sup>11</sup>

### Results

A total of 1,014 premenopausal women with self-reported heavy menstrual bleeding (mean age,  $41.7 \pm 6.8$  years; range, 22–65 years) met all inclusion and exclusion criteria and provided written consent to be enrolled at the 18 clinical sites between November 2010 and June 2012 (Figure 3). Of the consenting subjects 22 women withdrew or were withdrawn before entering the procedure room for the following reasons: subject withdrew consent, can-

celed, was lost to follow-up, or rescheduled for a later treatment ( $n = 14$ ), the control unit was unavailable ( $n = 2$ ), subject had financial or insurance concerns ( $n = 2$ ), presence of a patulous cervix ( $n = 1$ ), physician decision ( $n = 1$ ), and unknown reasons ( $n = 2$ ). The procedure was initiated in 992 enrolled subjects, with 931 who received a complete ablation. The 61 subjects who did not receive a complete ablation did not do so because of the following conditions: presence of preexisting anatomy which was incompatible with the procedure or device ( $n = 15$ ), preexisting uterine perforation discovered during initial hysteroscopy ( $n = 6$ ), technical malfunctions involving the equipment/console ( $n = 17$ ), patient intolerance (cramping, contractions, and/or discomfort) ( $n = 11$ ), evidence of a fluid leak at the cervix (none of which resulted in burns) ( $n = 10$ ), and a first-degree cervical burn ( $n = 2$ ).

Of the 992 subjects in whom ablation was initi-



**Figure 3**  
Status of study subjects.

ated, 4 (0.40% [95% CI 0.1–1.0%]) experienced thermal burns: 1 (0.10% [95% CI: 0.0%, 0.6%]) was clinically significant and was defined as a serious adverse device effect. The clinically significant burn occurred because of operator error: the system functioned properly until the patient moved under light sedation when the cervical seal became compromised. Three subjects' burns were reported as not clinically significant (3/992 [0.30%]). Details of each of the 4 burns and associated follow-up are provided in Table I.

Fifty-three (53/1,031 [5.1%]) technical malfunctions occurred in 44 procedures. The 53 technical complaints were associated with the following device components: 22 control units, 21 cassettes, 8 sheaths with tubing, and 2 others that were undefined. Twenty-two complaints or malfunctions resulted in abandonment of and incomplete endometrial ablation in 17 subjects. Of those 22 technical complaints that led to discontinuation of the

procedure, 9 were error messages, 8 were fluid loss alarms, 3 involved a fluid leak prior to the heating phase, 1 was a display/user interface problem, and 1 was undefined. None of the 8 fluid loss alarms was associated with a burn. Twenty (20/53 [37.7%]) of all the technical complaints occurred prior to the device coming in contact with the subject. Forty (40/53 [75.5%]) of the technical complaints occurred prior to the introduction of heated saline into the uterus. Twenty-seven (27/44 [61.4%]) subjects completed their procedures after 31 (31/53 [58.5%]) technical problems were addressed and resolved. Of the 17 procedures stopped due to a technical complaint, 14 were due to a fluid leak or inadequate seal, with a majority (n = 13) stopped prior to the delivery of heated saline.

### Discussion

This safety and device reliability study describes a low clinically significant burn rate of 0.1% in both

**Table II** Reported Thermal Burns by Case

Patient	Burn classification	Time of onset	Internal anatomy involved	External anatomy involved	Reported cause	Action taken	Medication given	Outcome
1	Superficial 2nd degree: clinically significant	During procedure	Vagina	Perineum	Inadvertent movement of the sheath as patient moved under light sedation with resultant hot fluid leak; poor cervical seal	Physician re-established seal and completed the ablation; burn was discovered post-operatively	Silver sulfadiazine ointment and metronidazole	Subject was discharged on day of procedure and at 3 weeks' follow-up was recovering with resolution of the burn
2	1st Degree: not clinically significant	During procedure	Cervix	No	Poor cervical seal	Incomplete ablation; burn was not apparent during or initially after the aborted procedure but was discovered at the 3-week follow-up with the evidence of nonodorous vaginal discharge and 2-cm ulceration on posterior lip of the cervix	Metronidazole gel	Subject was discharged on the day of the procedure and was recovering with resolution of the burn at the 21-day post-operative visit
3	1st Degree: not clinically significant	During procedure	Cervix	No	Poor cervical seal	Incomplete ablation; no medical action or intervention	None	Resolved without residual effects
4	Superficial 2nd degree: not clinically significant	During procedure	Cervix	No	Transfer of heat from the cervical seal to the cervical os	Ablation was completed as burn was not discovered until the 2-week follow-up	Prophylactic cephalixin and estrogen cream	Resolved without residual effects

intent-to-treat and evaluable populations. This low rate was reported during a proactive collection of treatment data and outcomes from a variety of clinical settings and from a large, geographically and age-diverse cohort of women with heavy menstrual bleeding who underwent hydrothermal ablation with the Genesys HTA System. Under rigidly defined parameters mandated by the FDA, this second-generation hydrothermal ablation system provided low burn rates of any kind in either the intent-to-treat ( $n = 992$  [0.4%] [95% CI 0.1–1.0%]) or evaluable ( $n = 931$  [0.2%]) [95% CI 0.1–0.8%]) groups.

In 2012 Brown and Blank described 7 years of nonresectoscopic endometrial ablation device complications as reported in the U.S. FDA Manufacturer and User Facility Device Experience Database through December 2011.<sup>12</sup> Their paper impresses the reader with two factors common to the complications, regardless of the device: lack of operator familiarity with the manufacturer's labeled instructions and/or inadequate training in correct device use. The rate of patient burns reported in our study was low, and the clinically significant burn rate was considerably less than the 0.42% projected by the FDA (by use of the voluntary system) and considerably less than the endpoint of 1% for clinically significant burns.

The robustness and strength of the study design were its inclusiveness of a broad geographic range and age range of patients and a broad geographic range and practice range of hysteroscopic surgeons to simulate normal clinical conditions. Limitations of the study were the collection of limited demographic data and the evaluation of burns only by the physicians with no requirement for photographs. Because the clinical and technical events were interpreted and reported by the physicians and the technical complaints were not analyzed according to a technical investigation of the device, we do not have a complete picture of the events. The technical complaint rate of 5.1% (53 out of 1,031 procedure sets) could be artificially inflated secondary to appropriate fluid loss alarms that may have been misinterpreted by sites as a technical complaint when in fact the device was performing as intended. What is certain is the considerably improved (decreased) rate of clinically significant burns (0.1%) from those reported for the first-generation device (0.8–1.4%).<sup>13–15</sup> This gain in safety can be attributed to the improved design features implemented in 2010.

Experience among device operators naturally

varies. There are those physicians who have had investigator opportunities to familiarize themselves with the device and procedure; they wholly understand the implications of any changes to the procedure and how those changes may affect patient welfare. There are also physicians who may not have as good interpretation of device cues out of lack of experience. We feel that this level of experience may have contributed to the burn rate, albeit a low one.

### Conclusion

The Genesys HTA System delivers a low rate of clinically significant burns and provides a safe and reliable treatment for premenopausal women with heavy menstrual bleeding.

### Acknowledgments

The authors thank Mimi Wainwright (Wainwright Medical Communications, Los Gatos, California) for assistance with the development of the manuscript; Meaghan Wilk and Benjamin Cutone of Boston Scientific (Natick, Massachusetts) for clinical support; and Yun Lu of Boston Scientific for statistical analysis of the study data.

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#### **Appendix A**

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