**EEFECTIVENESS AND SAFETY OF A NEW DISPOSABLE VAGINAL DEVICE FOR THE NON-SURGICAL MANAGEMENT OF PELVIC ORGAN PROLAPSE (POP) IN WOMEN**

**Abstract**

Hypothesis / aims of study:

A new disposable vaginal device for the management of POP was developed. The device is inserted vaginally in small dimensions within an applicator, by the user herself, at her home environment. Within the vagina the device opens to become a ring. Following insertion, the applicator is removed and discarded and the device may remain within the vagina for up to 7 days, when the user pulls a string and the device collapses and is comfortably removed from the vagina in small dimensions, for disposal. The user may insert the next device immediately or later, at her will.

The aim of the study was to evaluate effectiveness (objective & subjective) and safety of the new disposable vaginal device, when used by the user herself at her home environment.

Study design, materials and methods

The study was prospective, multi clinic, single arm, open label, hypothesis driven and statistically powered, home use performance study. Following screening and size fitting, device usage lasted 45 days, through visit 5. During that time subjects were allowed to use as many devices as they wished, for a period of 1-7 days each. During the device usage period, subjects had to fill out a diary, denoting each device’s usage length, functionality and adverse events.

Four almost identical device models were tested sequentially. Statistical analysis was done on results from all models. The 1st performance endpoint was the percentage of subjects with an improvement from baseline of at least 1 POP-Q stage.

Results

52 subjects completed the study per protocol in 3 clinics. 24 subjects completed one part of the study, 14 completed 2 parts, and 14 used the device during 3 parts, altogether 94 usage cycles in which 992 devices were used over 3393 usage days, an average of 36.1±5.70 days per subject.

66 subjects (70.2%) had POP-Q stage 3 prolapse, while 28 (29.8%) had stage 2 prolapse, at study start. At visit 5, 90 subjects (97.8%) had complete reduction of the prolapse (stage 0), while 2 subjects (2.2%) had stage 1 prolapse. Objective assessment showed that 100% of subjects had 2 POP-Q stages reduction while using the device and 97% of subjects with stage 3 prolapse (64/66) had 3 stages reduction (p<0.0001). Subjective assessment of POP related symptoms was carried out using an author compiled symptom score which showed mean improvement from 29 to 2.7 (P<0.0001). Modified PFIQ-20 QoL questionnaire showed significant improvement in QoL, from score of 33.6 to 5.1 (p<0.0001), and modified PFIQ-7 showed improvement from 24.9 to 0.7 (p<0.0001).

There were 91 device related adverse events (AE’s), recorded in a diary, and all recovered. There were no serious AE’s, most AE’s were mild (98.9%), of short duration and anticipated (87.9%), and included mainly spotting, discomfort and some pain. Most AEs occurred within 7 days from study start, and before using the first 5 devices (learning curve). There were no cases of vaginal infections, and there was only one case of urinary infection.

Satisfaction rate was high and most users considered the device as easy to use.

Concluding message

This new disposable vaginal device for the management of POP was found to be efficacious (with significant objective prolapse reduction and subjective relief of POP symptoms) and safe for use, with minimal mild and anticipated AE’s.

1. **Introduction**

**Pelvic Organ Prolapse (POP)**

While minor degrees of POP affect up to 75% of women who have had a vaginal delivery[[1]](#endnote-1), symptomatic POP with descent beyond the hymen affects 3% to 6% of the population[[2]](#endnote-2); ~10% of them will require surgery to correct the prolapse, of whom ~30% will require at least another one (1-5) operation[[3]](#endnote-3). Every year, 210,000 - 300,000[[4]](#endnote-4) women undergo surgical interventions for the disorder. It was estimated that within 30 years demand for services will grow by 45%, while the population will only grow by 22%[[5]](#endnote-5). The most commonly reported figure is that ~3.5 million USA women (range 1.36-5.33) currently suffer from symptomatic POP[[6]](#endnote-6). This figure equates to ~2.9% of the US female population over the age of 30, and is expected to rise 46% to 4.9 million by 2050.

**Vaginal Pessaries**

The most common non-surgical means of management of POP is insertion of a vaginal pessary, which is indicated for all pelvic prolapse stages[[7]](#endnote-7) and the most commonly used pessary is the ring-shaped. Pessaries are considered to be a relatively safe method of managing POP without serious side effects[[8]](#endnote-8),[[9]](#endnote-9),[[10]](#endnote-10). The ACOG practice bulletin recommends pessary trial use prior to any surgical management in patients with POP[[11]](#endnote-11).

Reports suggest that 76% of women can be successfully fitted within 1-4 pessary trials. Success or failure will depend on appropriate pessary selection, patient characteristics, provider training and experience, thorough counselling, as well as the achievement of an adequate fit and patient satisfaction.

Existing pessaries function well, but compliance to their use reduces over time. The median discontinuation rate was found to be 49.1% (37-80)[[12]](#endnote-12). The main reasons for discontinuation were inability to insert and remove the device, failure to retain the pessary, discomfort, desire to move to another mode of treatment (e.g. surgery), and sexual disturbances. Discontinuation tends to be higher among younger users who wish to achieve a final treatment for their condition[[13]](#endnote-13), while older women are more likely to adopt non-surgical solutions.

Pessaries have several features which limit their widespread use:

* All of them are reusable, made of plastic, hard rubber or silicones as resilient large bodies.
* Insertion of large noncompliant bodies is done manually, and is sometimes difficult, painful or unpleasant, in most cases necessitating a medical practitioner. Removal is sometimes hard, causing pain[[14]](#endnote-14) or discomfort.
* They are intended to remain in the vagina for prolonged periods of time, thereby causing irritations, pressure ulcers, infections, foul smelling discharge, etc.
* Many patients are reluctant to touch themselves in such intimate parts of their bodies, or are disgusted to clean the device, hence their reluctance to use it.
* Such reusable devices have a long standing bad reputation among patients and medical practitioners for being unpleasant, causing infectious discharge and foul odor, and being associated with disability and old age.
* Specific types of pessaries are linked to specific usage problems. Gellhorn device is more difficult for the users to use by themselves, and causes greater incidence of infectious discharge due to its shape[[15]](#endnote-15).
* The Cube pessary is the least used device because it adheres more to vaginal mucosa, which induces ulcers and secretions accumulation because as it fully occludes the vaginal canal. Also – intercourse is completely impossible without removal[[16]](#endnote-16).

**ProVate Device**

The ProVate Device is a vaginal ring pessary designed to perform exactly as the existing ring pessary, while reducing or even eliminating most of the problems mentioned above. It is made of a flexible skeleton covered by a soft elastomer. The following features for the ProVate Device were designed to overcome specific shortcomings of existing pessaries, making the new support a user-friendly device:

* A single use device (disposable), avoiding the need for cleaning and using a reusable device, thus reducing disgust, infections, and smells. The device may be left in place for up to 7 days.
* Supplied clean, ready for use, for immediate insertion (resembling the menstrual tampon).
* Insertion and removal become much more comfortable and painless, by minimizing the dimensions of the device during insertion and removal. The device is compressed in an applicator during insertion and collapses when the removal string is pulled. Deployment of the ring support happens while it is already within the vagina, hence there should be no or minimal discomfort around the introitus during its passage.
* An intuitive well known procedure for many women, resembling insertion and removal of the menstrual tampon.
* Available for home use at the user’s own discretion.
* A minimal self-touch procedure.
* No interference with daily life style, device can easily be removed by the user for sexual intercourse.
* The device is provided in 6 sizes

Size fitting of the ProVate device is performed by a medical practitioner at the office, following the same clinical routine as with existing vaginal pessaries. However, it may be somewhat easier than with other marketed pessaries since the device is disposable and thus size fitting may be performed with the actual ProVate Device.

Figure -The ProVate Device

Figure 1 shows the ProVate Device in different configurations, compacted and deployed, with and without the applicator, within and outside the body.

|  |  |
| --- | --- |
|  | 07.tif |
| Figure 3b-The ProVate support, within its applicator, inserted intra-vaginally. | Figure 3a The ProVate support, in its compacted mode |
| 09.tif |  |
| Figure 3d-The ProVate support in its deployed (ring shape) mode, during use | Figure 3c-The ProVate support in its narrow compact mode, without the applicator. |
|  | |
| Figure 3e-The ProVate support in its narrow compact mode, pulled out of the vagina for disposal | |

Figure 1-The ProVate Device in different configurations

1. **Materials & Methods**
   * 1. **Study objective and Endpoints**

Study was a pivotal study for the assessment of safety and effectiveness of the *ProVate* vaginal pessary. The study was designed to test up to four (4) *ProVate* device models in an iterative fashion***.*** Minor design improvementswere made to each of the models tested, mainly to the applicator system, based on the experience gained from the usage of the previous model. The objective of the study was to confirm that the ProVate Device, intended for home self-use, is effective and safe during regular use.

The study was designed as a prospective, multi clinic, one arm, open label, non-randomized, non-controlled, R&D supporting, home use performance study.

*Study Endpoints were:*

1. ***Performance***

**Primary endpoint**

The primary Endpoint of this study was the proportion of subjects with an improvement from baseline of at least 1 stage in the POP-Q scale at visit 5.

**Secondary endpoints**

1. Effectiveness: the change from baseline in stage of prolapse assessed by the POP-Q scale at visit 5 and at the various visits, and POP symptoms change during the study as assessed by the POP symptom questionnaire. Also, assessment of prolapse grade was done using the Baden and Walker Halfway Grading.
2. Quality of Life (QoL): Change from baseline in quality of life as assessed by the modified PFDI-20 and PFIQ-7 questionnaires
3. Various functional aspects of the device
4. Satisfaction and ease of use

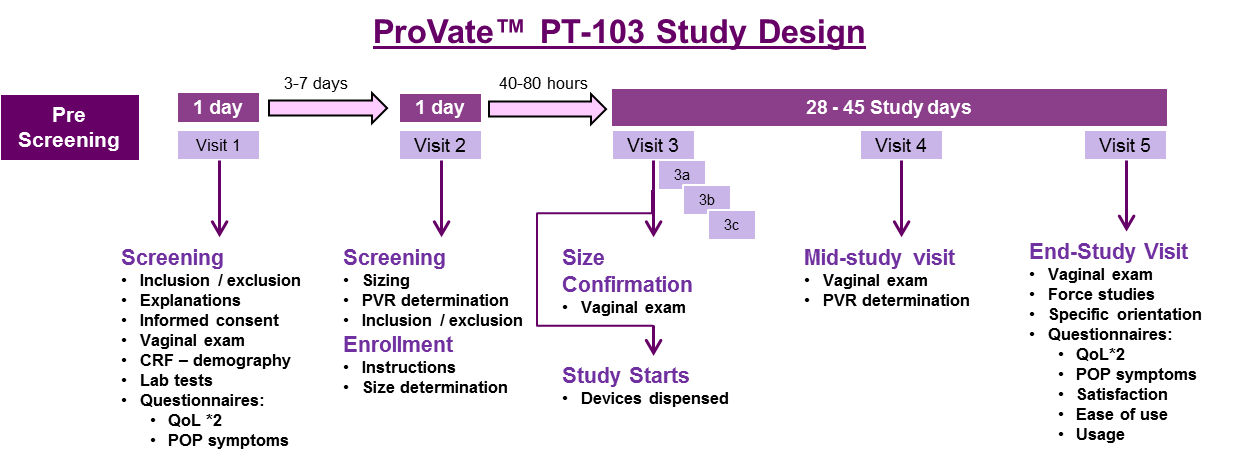
**2. Safety**

1. Rate and incidence of anticipated Adverse Events (AE). Anticipated AE’s include:
   * 1. Vaginal wall trauma (e.g. erosions, abrasions, ulcerations), Vaginal/Urine infection, Pain, Bleeding, Discomfort, de-novo or worsening urinary incontinence and Constipation.
2. Rate and incidence of Serious Adverse Events (SAE), rate and incidence of all AE’s (anticipated and non-anticipated, serious and non-serious, related and unrelated to the study device), and rate and incidence of device intactness.

Study population included female subjects, aged 21 to 80 years, who were in good general health and suffered from symptomatic POP of any vaginal wall (POP-Q stage 2-4).

The study was conducted in three (3) clinics (Gynecology & Urogynecology) in Israel.

Study consisted of 5 distinct stages: Screening, Enrollment, Size fitting, Device usage and Termination. Figure 2 below demonstrates study design.



Inclusion/Exclusion evaluation was based on the subject's medical background, pelvic examination (presence of vaginal wall prolapse, vaginal atrophy, etc.), and laboratory tests results conducted at the screening visit (visit 1 and the first part of visit 2). Once criteria was verified, the candidate was offered to participate in the study and attend visit 2.

Figure 2-Graphic display of the study plan

Inclusion Criteria included the following: Females aged 21-80 years, ability to use both hands and insert a device into the vagina, a symptomatic sensation of vaginal prolapse, ability to attend the study clinics during the study and ability to understand the nature of the study and sign an informed consent. On examination, a POP-Q stage 2 – 4 prolapse should be demonstrated, of one or more sites along the vagina. Also, a 61-91 mm pessary should be well fitted and retained.

Exclusion Criteria included previous inability to accommodate tampons or vaginal pessaries, current participating in another clinical study, co-morbid condition(s) or severe systemic disease that could limit the subject’s ability to participate in the study, or impact the scientific integrity of the study, pregnancy, or suspected pregnancy or intension to be pregnant during the course of the study, abnormal vaginal bleeding in the past 6 months, previous vaginal surgery during the last 3 months, severely atrophic vagina, existing vaginal or vulvar laceration, symptomatic vaginal or urinary tract infection as determined by physical examination and lab results, recurrent urinary tract infections and abnormal cervical cytology.

The following hypothesis was tested:

* H0: PPOP-Q<70%
* H1: PPOP-Q≥70%

where PPOP-Q is the proportion of subjects with an improvement from baseline of at least one stage as determined by the POP-Q.

The full analysis set (FA) includes all subjects who were enrolled and for whom the study device insertion was initiated (even if the insertion process was never completed). The FA analysis set served as the main analysis set for safety assessments. The per-protocol analysis set (PP) includes all subjects from the FA analysis set, who used the study device models for at least 20 days, without any major protocol deviation. The PP analysis set served as the main analysis set for the effectiveness and performance analyses.

Statistical analyses were performed using SAS v9.4 (SAS®, SAS Institute Cary, NC USA) software. The required significance levels of findings are equal to or lower than 5%. All statistical tests were two-sided, if not defined otherwise. Where confidence limits are appropriate, the confidence level was 95%.

1. **Study Results**

In the Initial part of the study (part A), 44 subjects enrolled and tried the device at least once (FA set). 33 subjects completed the study per protocol (PP set). Minor amendments were made to the applicator system, and this was tried during part B of the study where 20 subjects who also participated in part A tried two slightly amended applicator system models. All 20 subjects completed the study. The final finished product was tried again by 47 subjects in part C of the study (22 who participated in at least one previous part, and 25 new recruits). 41 subjects completed part C of the study. Subject disposition may be seen in Figure 3.

In total, 52 subjects completed the study in 3 clinics. 24 subjects completed one part of the study, 14 completed 2 parts, and 14 used the device during 3 parts. Altogether, in the Per Protocol set, there were 94 usage cycles in which 992 devices were used over 3393 usage days, an average of 36.1±5.70 days per subject. In the Full Analysis set (safety), 1592 devices were used over 3558 study days.

94 subjects completed the study per protocol. Within the 94 usage cycles (per protocol set), mean number of devices per subject was 10.6±3.42 [6-26], and mean device usage period was 3.4±2.23 [7-27] days. Mean usage length per subject was 36.1±5.70 days.

* + 1. **Subject Disposition Probably will give-up this figure**

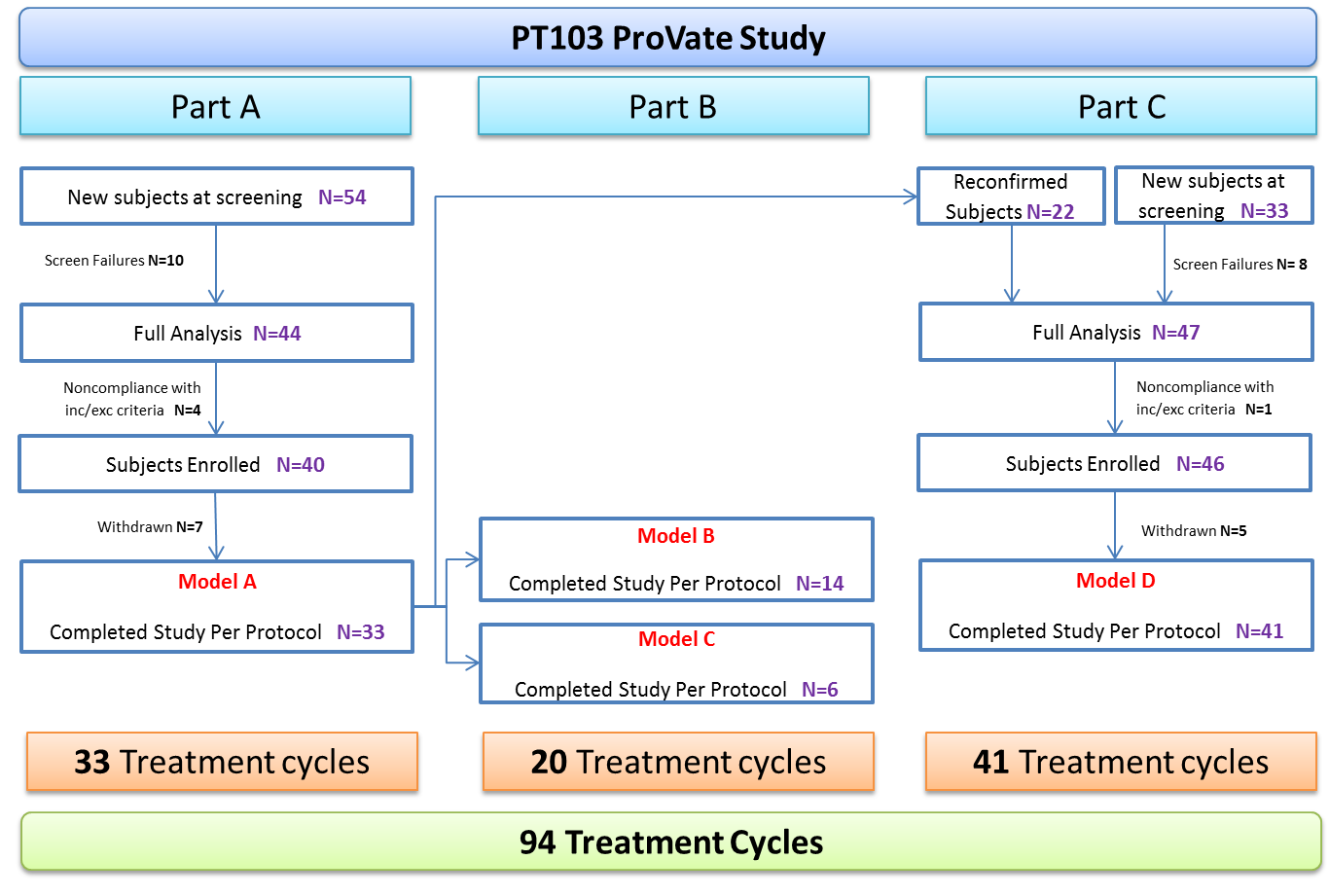


Figure 3-Subject disposition within the PT103 study, with its 3 different parts

* + 1. **Subjects’ Baseline Characteristics**

Table 1 below shows subjects baseline characteristics (Full Analysis set (FA))

Perhaps we should reduce into a paragraph, not a table

|  | **PT 103 Study (FA)** | |
| --- | --- | --- |
|  |  | **All Cohorts** |
| Mean Age (years) |  | 60.4±9.72 (range 33.2-80.3) |
| Age group |  |  |
| <50 |  | 20 (18.0%) |
| 51-60 |  | 22 (19.8%) |
| 61-70 |  | 58 (52.3%) |
| 71-80 |  | 11 (9.9%) |
|  |  |  |
| Mean Weight (Kg) |  | 69.9±12.59 (range 54-100) |
| Mean height (cm) |  | 164.5±6.46 (range 145-176) |
| Mean BMI |  | 25.8±4.46 (range 19.0-40.6) |
| Deliveries |  | **151** |
| spontaneous |  | 108 |
| Instrumental |  | 39 |
| Caesarean |  | 4 |
| Mean newborn Weight (gr) |  | 3662±449 (range 2600-4850) |
| Menopausal status |  |  |
| postmenopausal |  | 90 (81.1%) |
| perimenopausal |  | 1 (0.9%) |
| premenopausal |  | 20 (18%) |
| Mean length of amenorrhea (Y) |  | 14.2 (range 1-28) |
| HRT usage (# of users) |  | 13 (11.7%) systemic,  6 (5.4%) local vaginal |
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Table 1-Characteristics of subjects within the PT103 study (FA)

129 subjects were screen for the 3 parts of the study, 111 enrolled, and 17 (15.3%) prematurely discontinued the study. Reason for premature termination included Adverse Events (low extremities pains (1), DeNovo SUI (1) and discomfort (1)), inability to insert the device by the user herself (2), wish for surgery (1), inability to be fitted with available device’s size (8), protocol violation (3).

In 8/111 cases, (7.2%), subjects could not be fitted with a proper size device. In 94/111 cases (84.6%), a proper size device was found. There was a very little change in device sizes along he study, when average device sizes at visits 2-5 were compared with final device sizes at visit 5. This may represent he fact that the proper device size is found at an early usage stage, in most cases.

* 1. **Results from the Pooled Analysis (All Cohorts)**

***The Primary Effectiveness Endpoint was “The proportion of subjects with an improvement from baseline of at least 1 stage in the POP-Q scale, at visit 5”.***

During the screening visit, within the PP set, 28 subjects had POP-Q stage prolapse, while 66 subjects has POP-Q stage 3 prolapse. Following insertion of the device, the prolapse was reduced substantially, as may be noted in Table 2, and in visit 5, 90 subjects had no prolapse (POP-Q stage 0), and 2 subjects had POP-Q stage 1 prolapse.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Visit** | **POPQ stage 0** | **POPQ stage 1** | **POPQ stage 2** | **POPQ stage 3** | **POPQ stage 4** |
| **Screening** |  |  | ***35 (31.5%)***  **28 (29.8%)** | ***76 (68.5%)***  **66 (70.2%)** |  |
| **Visit 3** | *93 (96.9%)*  89 (96.7%) | *3 (3.1%)*  3 (3.3%) |  |  |  |
| **Visit 4** | *93 (96.9%)*  91 (96.8%) | *1 (1.0%)*  1 (1.1%) | *2 (2.1%)*  2 (2.1%) |  |  |
| **Visit 5** | *90 (97.8%)*  **90 (97.8%)** | *2 (2.2%)*  **2 (2.2%)** |  |  |  |

Table 2-All Cohorts - comparison of POP-Q stages before (screening) and while using (V5) the Device, (FA (red) PP (black), p<0.0001)

100% of subjects had at least one stage improvement in the POP-Q scale (in both PP and FA sets) while wearing the ProVate device. The p-value for the exact binomial test is <0.0001. Therefore, the null-hypothesis (=70%) is rejected and it is concluded that the percent of subjects with an improvement from baseline of at least 1 stage using the ProVate Device is statistically significantly greater than 70%, thus the success criterion is met in both analysis sets. This improvement was shown at all 3 sites with no statistically significant difference, hence all study sites were pooled and analyzed as one.

Overall the proportion of subjects in the PP set with improvement from baseline of at least one stage in POP-Q was 100% at all visits. In particular at visit 5, the lower 95% confidence limit is 96.1% and thus we may claim that this rate is greater than 96.1% with 95% confidence.

The primary performance assessments were also performed on the entire FA set, as a sensitivity analysis, including subjects for whom no POP-Q measurement was available after baseline. Overall, this success rate was 94.59% (105/111), with a 95% confidence interval of [88.61%; 97.99%] and a p-value of <.0001 for the exact binomial test of the null hypothesis (Null value = 70%). Thus, the success criterion is met in this sensitivity analysis as well.

***The 1st Secondary effectiveness Endpoint was “the change from baseline in stage of prolapse assessed by the POP-Q scale at visit 5. An acceptable outcome for this endpoint will be to show that the mean improvement is greater than one (1) stage”***.

Table 3 show results for the All Cohorts population, demonstrating that 100% of ProVate Device users (PP) had a reduction of at least 1 POP-Q stage while using the device, 100% of ProVate Device users also had at least 2 POP-Q stages reduction while using the device and 64/66 of users with POP-Q stage 3 prolapse (97%) had even 3 POP-Q stages reduction while using the device.

This change was shown to be significant with all p-values<0.0001, demonstrating that the ProVate Device significantly reduces the prolapse.

|  |  |  |  |
| --- | --- | --- | --- |
| **change** | **At least 1 POPQ stage**  **reduction** | **At least 2 POPQ stages reduction** | **3 POPQ stages reduction** |
| Visits 1-5  [95% Exact CI\*] | 94/94 **(100%)**  [96.15; 100] | 92/92 **(100%)**  [96.07; 100] | 64/66 **(97.0%)**  [89.48; 99.63] |

Table 3 -% of cases in which a reduction of prolapse occurred while using the ProVate Device (PP, All Cohorts, P<0.0001)

Results from the study show that the mean change from baseline in POP-Q scale ranged between 3 and 2 points at all visits throughout the study, statistically significantly different from “1”, at all visits. Therefore, this endpoint is met.

***The 2nd Secondary Effectiveness Endpoint was POP symptoms change during the study as assessed by the POP Symptom Questionnaire.***

POP related symptoms score was devised by ConTIPI Medical Ltd. (Caesarea, Israel) as an author compiled questionnaire. POP related complaints (symptoms) were graded 0-4 (0 being “no complaint at all” and 4 being “significant complaint”), and scores during visit 1 (before using the device) and visit 5 (while using the device) were analyzed and compared. Results were normalized to the 100 scale.

Figure 4 shows results for the POP Symptom Score obtained from visit 1 (prior to device use) and visit 5 (while using the ProVate). All POP related complaints were significantly reduced while using the ProVate Device. The Mean total scores was reduced from 29 to 2.7 (p-value of the means<0.0001).

Additional analysis evaluated the percentage of subjects who had no complaints following the use of the ProVate device. In the All Cohorts population, between 73.4% and 97.9% of the subjects reported no symptoms at all at the end of usage visit in comparison with a range of 11.7% to 94.7% who had no complaints at the screening visit.

Figure 4-Comparison of POP related symptoms average scores before using the ProVate Device and while using the device (PP, All Cohorts, p<0.0001)

* + 1. **Quality of Life (QoL) questionnaires**

**Modified PFDI 20**

The entire validated PFDI-20 questionnaire includes questions on various pelvic floor disorders which are beyond the scope of this study; hence subjects were requested to respond only to questions that are pertinent to POP. In this modified score, 10/20 questions of the original PFDI-20 questionnaire were utilized. Possible scores in this questionnaire were 0-4, where 0=not at all, 4=very much. Results were normalized to the 100 scale.

Results shown in Figure 5 demonstrate statistically significant decrease in all modified PFDI-20 items (which implies improvement in QoL regarding POP). The difference between visit 1 and visit 5 of 28.52 (SD=20.31) in mean total score of the modified PFDI-20 questionnaire is statistically significant (p<.0001).

Figure 5-Comparison of the Modified PFDI 20 average Score before using the ProVate Device (Visit 1) and while using the device (Visit 5) (PP, All Cohorts, p<0.0001)

Overall, within the All Cohorts population, the percent of subjects reporting that they had no problem (scored “not at all” for specific items of the PFDI-20 questionnaire) ranged between 5.3% and 76.6% at baseline but increased to 80.6% through 98.9% at the end of usage period.

**Modified PFIQ-7**

The entire validated PFIQ-7 questionnaire includes questions on various pelvic floor disorders which are beyond the scope of this study; hence subjects were requested to respond only to questions regarding POP (Modified PFIQ-7). Possible scores in this questionnaire were 0-3, where 0=not at all, 3=very much. Results were transformed to a scale of 0-100.

Comparison of scores during visit 1 (before using the ProVate Device) and scores at visit 5 (while using the ProVate Device) of this modified PFIQ–7 show significant difference (improvement in QoL regarding POP) for all questionnaire items. The mean total PFIQ-7 score was 24.9 at visit 1 and 0.7 at visit 5, (P<0.0001).

Figure 6-Comparison of PFIQ-7 scores from before and while using the ProVate Device.

Overall the percent of subjects reporting no symptoms at all increased from between 33.0% and 81.9% to 95.7% at least from the screening to visit 5. Overall the mean total score was 24.9 at visit 1 versus 0.7 at visit 5. Overall the difference between visit 1 and visit 5 of 24.16 (SD=23.87) in mean total score of the PFIQ-7 questionnaire is statistically significant (p<0.0001).

***Adverse Events***

General safety analyses were conducted on the Full Analysis Population (FA).

Table 4 shows breakdown of AE’s into Non-Device Related (NDRAE) and to somehow Device-Related (DRAE), further splitting into Remotely, Possibly, and Probably Related sub-groups the Pooled Analysis (Full Analysis set).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Population | Total AE | Non-Device Related AE  (NDRAE) | Device Related Adverse Events (DRAE) | | | |
| Remotely | Possibly | Probably | Total DRAE |
| All Cohorts | 124 | 33 (26.6%) | 8 (6.5%) | 17 (13.7%) | 66 (53.2 %) | 91 (73.3%) |

Table 4-Number & percentage of device-related and non-device related adverse events (FA,All Cohort)

Adverse events were reported in one of the following methods:

* By using a diary
* During a scheduled meeting with the investigator
* During a non-scheduled call from the subject to the clinics
* During a scheduled weekly telephone call to the subject

In the Pooled Analysis (All Cohorts), 124 adverse events were reported related to 62/111 FA subjects (55.9%). 91 device-related AEs were recorded by 50/111 subjects (45%). Most device-related AE’s (80/91; 87.9%) were anticipated.

* One (1 (0.8%)) AE was recorded before study started.
* Three (3 (2.4 %)) AEs was recorded during the Screening phase.
* Thirty eight (38 (30.6%)) AEs occurred during the Sizing and Size Confirmation phases.
* Eighty two (82 (66.1%)) AEs occurred during the Device Usage phase.

91/124 (73.3%) AEs were determined to be potentially related to the device (in 50 subjects):

* Thirty three (33 (36.3%)) AEs were recorded during the sizing phase
* Fifty eight (58 (63.7%)) were recorded during the entire device usage phase

There were no device-related SAEs.

*In the All Cohorts population (FA set) there were 91 device-related adverse events while using* ***1592*** *devices over* ***3558*** *usage days*

Figure 7 shows the frequency of the various adverse events reported within the study, which were recorded on a daily basis.

Figure 7-Ferquency of the types of Device Related AE’s within All Cohorts, further divided into anticipated and non-anticipated (FA)

It is clearly seen that most of the AE’s occurred during part A of the study where all subjects had no experience with the device. This figure shows that AEs reduce considerably while gaining experience with the device (“learning curve”).

As expected, the most common AE’s were discomfort and spotting, which are anticipated for all devices that are used vaginally. Vaginal wall trauma was only seen at part A of the study, not seen again following proper training by the investigators. The largest part of the AE list consists of sporadic AE’s, usually of 1-2 complaints each.

Adverse Events Intensity

In the All Cohorts population- most of the AE’s (117/124; 94.4%) were considered mild. 7/124 AE’s were considered moderate, including Pneumonia, Confusion, Tooth Extraction, Wrist fracture, Presumptive UTI (treated by the family physician without urine culture, without notifying the site), and Asymptomatic Bacteriuria.

Action taken regarding study device

All AE’s (100%) completely resolved with no sequelae. None of the AE’s was ongoing when the study was concluded.

Adverse Events and length of device usage

The ProVate device is intended for usage of up to 7 days. Altogether there was a low rate of device related AE’s during the study, and as expected, most device related AE’s occurred during the first duration of usage and tended to decrease along usage. No excess AE’s were observed when devices were used for 3-5 days, 5-7 days, or >7 days.

Accommodation curve

As with other vaginal devices, a learning/accommodation period, during which subjects become accustomed with the device, was expected. Most AEs occurred during the sizing phase (where the subjects became aware of the new device) and during the beginning of the usage phase (where subjects became accustomed with the device). It was clear that AEs were reduced while subjects became more experienced with device usage.

Most of the device-related adverse events occurred within up to one week from visit 3 (58.9%) (Figure 8).

Most of the device-related adverse events occurred while using the first 5 devices (75.5%) (Figure 9).

Weeks from visit 3

AEs

Figure 8-Break down of Device Related AE’s by weeks from visit 3 (FA, all cohorts)

Repeated users vs. new users

As anticipated, experience with the device substantially reduces device relates AE’s. 83.5% of the AEs at least remotely related to the study device were reported among new users (had no previous experience with the device).

Figure 9-Break down of Device Related AE’s by the number of device in the study (FA, cohort D in blue, all cohorts in red))

* + 1. **Discussion of Specific Safety points** 
       1. ***Rate of vaginal infections***

During the ProVate study no subject had vaginal infection

* + - 1. ***Rate of urinary infections***

Urinary tract infection (UTI) is not rare in women, mainly in postmenopausal women, and specifically – women with POP are more prone to having UTI’s.

* There was one case in part B of the study where the subject complained of having slightly red urine (without any other complaints). Initial culture showed no infection, but repeated culture showed E Coli 104. She received antibiotics and the study was delayed until urine was clear and MSU was normal.
* There was one case within part A of the study where a subject was treated by her general practitioner with antibiotics for presumed UTI, without reporting to the study site.
  + - 1. ***Signs of urinary retention (by US).***

Post-Void Residual (PVR) urine volume was studied by ultrasound scan before insertion of the first device, and with the device deployed within the vagina. Before using the device, mean PVR was 15.0±15.56 ml (range 0-53.5 ml). While using the device, during visit 4, mean PVR was 14.1±21.9 ml (range 0-90.7 ml). There was no significant difference in PVR before and while using the ProVate Device.

1. **Discussion**

POP is mainly a quality of life condition, and in most cases treatment is not mandatory, but a choice. Therefore, management should be tailored to suit needs and perceptions of different women

Vaginal ring pessaries are used for the non-surgical management of POP for many years. In fact, they function well in most cases, provide mechanical support and substantially reduce vaginal wall prolapse. However, logistics around them may be cumbersome and even bothering, as by being reusable they require constant medical care (cleaning and replacement) and are associated with vaginal discharge, odors and infections, perception of aging and disability, and functional sexual disturbances (intercourse may be disrupted/impaired or even impossible with the device). Only a rather small fraction of pessary users are able to remove and replace the pessary, hence the dependency upon the medical system.

The ProVate Device is a disposable flexible vaginal ring pessary designed to overcome many of the faults of existing ring pessaries, described above. It is designed to allow the users to insert and remove it by themselves, at their home environment, at their own discretion. The concept behind the development of the ProVate Device allows women to take control over their POP management (ability to decide when and where to insert or remove the device by themselves, always a fresh device with no need for cleaning) and over their intimate behavior (constant ability to remove the device prior to intercourse, and reinsert a new one afterwards).

* 1. **Efficacy**

Being mainly a quality of life issue, success rate of any POP management may be discussed in two manners – anatomical reduction of prolapse, and alleviation of prolapse symptoms. There are many cases in which anatomical correction does not alleviate prolapse symptoms, hence the importance of recording both points.

Reduction to stage/grade zero (0) was achieved in over 94% of subjects, and for the rest (6%), reduction to stage/grade one (1) was achieved. Also, all subjects had a reduction of at least 2 stages, and in most of the subjects with stage 3 prolapse – even 3 stages/grades prolapse reduction. These results were also achieved when the ProVate Device was inserted in a different orientation (45-90°), to mimic potential user error.

Level of complaints before the study and while using the ProVate Device were compared and a significant improvement was noticed while using the device (p<0.0001).

Quality of life has increased considerably and significantly while using the ProVate Device. This was reflected by employing the two validated Pelvic Floor QoL Questionnaires – PFIQ-7 and PFDI20 (modified).

These achievements are comparable to results achieved while using existing vaginal pessaries, as both devices function similarly. McIntosh et al (2016)12 concluded that 85% of women may have relief of POP symptoms while using a pessary. **This is very much** comparable to the PT103 study results discussed above.

* 1. **Safety**

When a woman initially uses any intra-vaginal device, it is common to note that the first period of usage is accompanied by some discomfort and, occasionally, other mild adverse events. This period is a learning and accommodation period, in which the user gains an understanding as to how to place the device properly and becomes accustomed with its sensation. In most cases, this is also the time of the “size fitting”, in which the correct size for her is evaluated by the clinician, and she gets used to the device. Complaints, or AE’s, which are anticipated at that time of accommodation, may include discomfort, spotting, pain and/or some bleeding.

The medical literature cites conflicting data on the prevalence of AE’s within groups of pessary users. While Hanson et al[[17]](#endnote-17) report only 14.5% of any complaints within pessary users; Bai et al[[18]](#endnote-18) report 73.1% adverse events, while West & Moore21 found 56% adverse events with pessaries (including bleeding, purulent foul smelling discharge, severe discomfort, constipation and urinary symptoms). This huge variability in complication rate most likely reflects a difference in reporting. An ongoing daily/weekly follow-up of complaints and findings among users, as was employed in this study, will likely lead to much larger proportion of complaints, as compared with retrospective reporting. However, despite fairly high rate of minor complications in the literature, many users who are well fitted with pessaries report being satisfied with this management and wish to continue its use, hence pointing out that these complications/complaints are minor.

In this study, subjects were requested to hold a very strict daily diary, in which they had to report on every feeling, or adverse events they had. This tight AE’s recording is unique to this study and does not reflect the way AE’s are recorded in most other published reports on existing pessaries.

Vaginal wall trauma, a very well-known and described adverse event of pessary usage, occurs in 19.3% of long term pessary users[[19]](#endnote-19) (range 3-24%[[20]](#endnote-20).) Within the PT103 study, there were 7 cases of erosions, only in part A of the study, which were noted by the investigator only (not the subjects), and were believed to be caused by the initial trials to insert the device. Following better understanding of how to insert the device – no vaginal wall trauma was diagnosed nor complained of, during parts B and C of the study. This is further explained by better insertion techniques and the regular replacement of fresh devices.

Urogenital infections are rather common in women. However, during the PT103 study;

* Altogether – there were no subject’s complaints re signs and symptoms of vaginal infection.
* No subject was diagnosed with vaginal infection within the PT103 study where 1592 devices were used over 3558 days.
* A survey of 2000 women in the US found that 10.8% of women >18 years reported at least 1 presumed UTI during the last 12 months[[21]](#endnote-21). In postmenopausal women – this figure becomes substantially higher. In the PT103 study, there was only one case of symptomatic UTI, and one case of presumed UTI in postmenopausal women, which may or may not be attributed to the ProVate Device.

As expected, there are several important safety findings arising from the PT103 study:

* Most device-related AE’s occurred during usage of the first 5 devices. This finding is not specific, and is attributable to the learning curve needed to become acquainted with the correct insertion and placement of the device.
* Most AEs were reported within the week following study start (again, first usages).
* Most device-related AE’s were anticipated (>85%).
* Almost all AE’s were mild, and of short duration, which resolved without sequelae and without medical intervention, except for one case of presumptive UTI, one case of UTI, and one case of Asymptomatic Bacteriuria (non-device related).
* There were no severe/serious device-related AE’s.
* There were no cases of vaginal infection.
* There was no interference with normal body functions – no complaints regarding disruption of bowel movements, and no objective evidence of residual urine.

**Taking the above mentioned anticipated, mainly mild, device related AE’s, and absence of neither clinical vaginal infections nor interference with body functions, we may conclude that the ProVate Device is safe for use**

* 1. **Continuation rate and user’s ability to control management of POP**

In most cases of pessary usages, the user is unable to insert or remove the device by herself, and in a study among 496 British Gynecologists, many of them said that besides other reasons for pessary discontinuation, 10.7% of the users did so because of “dislike of the changing procedure”15. In a cohort of 7 studies, discontinuation rate was 49.1% (range 37-80), with the main reasons expulsion of the pessary, discomfort, desire for surgery and inability to insert/remove the device by the user.

Overall, in the PT103 study, 17 (15.3%) subjects discontinued the study, 8 because no size was available for them and 3 due to non-compliance with study protocol. Only 3 subjects dropped for AEs, one subject decided upon surgery and 2 subjects due to inability to insert the device into the vagina.

Disposable home self-use devices, such as the ProVate device, may allow women to use the device when they choose, and for their preferred allowed length of time. This was described by women in the study as “freedom to decide”.

The ability to control POP management was noted verbally by the study subjects during the visits to the clinic:

* The ability to have unhindered intercourse at their own time and wish – which only required a pull on the string, and inserting a new device later. This is barely possible when using an existing ring pessary which almost always requires removal and replacement by a medical practitioner.
* The ability to have some “device free intervals” – some women felt that they don’t need to have a new device inserted immediately following removal of the previous one, and enjoyed some time of POP-symptom-free periods, which allowed them to remain without a vaginal device for some time, until they felt the need to insert a new device.

1. **Conclusions**

The primary and all Secondary endpoints of the PT103 study were successfully achieved and addressed, covering efficacy, safety, functionality and quality of life.

It has been shown that the ProVate Device is:

* Effective - since the null-hypothesis was rejected, and as demonstrated by the anatomical correction of the prolapse and alleviation of symptoms
* Safe for use - as there was no major safety concern due to adverse events, all device related adverse events were minor and the majority of them were mild and anticipated.

1. **References**

1. Nygaard I, Barber M. Prevalence of symptomatic Pelvic floor disorders in US women. JAMA. 2008 September 17;300(11)1311-1316 [↑](#endnote-ref-1)
2. Swift S, Woodman P, O’boyle A et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192(3):795-806. [↑](#endnote-ref-2)
3. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol, 1997;89:501-506. [↑](#endnote-ref-3)
4. Barber MD, Brubaker L et al: Comparison of 2 trans-vaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse. JAMA;2014;311(10):1023-1031 [↑](#endnote-ref-4)
5. Luber KM, Boero S, Choe JY:The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol 184(7):1496-1501. Discussion 1501-3. [↑](#endnote-ref-5)
6. Wu JM, Hundley AF, Fulton RG, Myers ER. Forecasting the prevalence of pelvic floor disorders in USA women, 2010-to 2050. Obstet Gynecol 2009:114(6): 1278-1283 [↑](#endnote-ref-6)
7. McIntosh L (2005) The role of the nurse in the use of vaginal pessaries to treat pelvic organ prolapse and/or urinary incontinence: a literature review. Urol Nurs 25(1):41–48 [↑](#endnote-ref-7)
8. Atnip SD. Pessary use and management for pelvic organ prolapse. *Obstetrics & Gynecology Clinics of North America*. 2009; 36(3): 541-63 . [↑](#endnote-ref-8)
9. Hanson LAM, Schulz JA, Flood CG, Cooley B, Tam F. Vaginal pessaries in managing women with pelvic organ prolapse and urinary incontinence: Patient characteristics and factors contributing to success. *International Urogynecology Journal and Pelvic Floor Dysfunction*. 2006; 17(2): 155-159. [↑](#endnote-ref-9)
10. Vierhout ME. The use of pessaries in vaginal prolapse. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 12004; 17(1): 4-9. [↑](#endnote-ref-10)
11. Committee on Practice Bulletins-Gynecology, American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 79: Pelvic organ prolapse. Obstet Gynecol. 2007;109(2 Pt 1):461-473. [↑](#endnote-ref-11)
12. Coelho SCA, De Castro EB, Juliat CRT: Female pelvic organ prolapse using pessaries: systematic review. Int Urogynecol J DOI 10.1007/s00192-016-2991-y [↑](#endnote-ref-12)
13. Mamik MM, Rogers RG, Qualls CR, Komesu YM (2013) Goal attainment after treatment in patients with symptomatic pelvic organ prolapse. Am J Obstet Gynecol 209(5):488.e1–488.e5 [↑](#endnote-ref-13)
14. # [Taege SK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taege%20SK%5BAuthor%5D&cauthor=true&cauthor_uid=28594757), [Adams W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Adams%20W%5BAuthor%5D&cauthor=true&cauthor_uid=28594757), [Mueller ER](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mueller%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=28594757), [Brubaker L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Brubaker%20L%5BAuthor%5D&cauthor=true&cauthor_uid=28594757), [Fitzgerald CM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fitzgerald%20CM%5BAuthor%5D&cauthor=true&cauthor_uid=28594757), [Brincat C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Brincat%20C%5BAuthor%5D&cauthor=true&cauthor_uid=28594757). Anesthetic Cream Use During Office Pessary Removal and Replacement: A Randomized Controlled Trial. [Obstet Gynecol.](https://www.ncbi.nlm.nih.gov/pubmed/28594757) 2017 Jun 6. doi: 10.1097/AOG.0000000000002098

    [↑](#endnote-ref-14)
15. Cundiff GW, Amundsen CL, Bent AE, Coates KW, Schaffer JI, Strohbehn K et al (2007) The PESSRI study: symptom relief outcomes of a randomized crossover trial of the ring and Gellhorn pessaries. Am J Obstet Gynecol 196(4):405.e1–405.e8 [↑](#endnote-ref-15)
16. Kuhn A, Bapst D, StadlmayrW, Vits K, MuellerMD(2009) Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful? Fertil Steril 91(5):1914–1918 [↑](#endnote-ref-16)
17. Hanson LA, Schultz JA, Flood CG, Cooley B, Tam F:Vaginal pessaries in managing women with pelvic organ prolapse and urinary incontinence; patient characteristics and factors contributing to success. Int Urogynecol J pelvic floor Dysfunct 2006;17(2):155-9 [↑](#endnote-ref-17)
18. BAI SW, Yoon BS, Kwon JY, Shin JS, Park KH et al. Survey of the characteristics and satisfaction degree of the patients using a pessary. Int Urogynecol J pelvic floor Dysfunct 2005;16(3):182-6 [↑](#endnote-ref-18)
19. Ramsay S, Tu LM, Tennenbaum Cara. Natural History of pessary use in women aged 65-74 versus 75 years and older with pelvic organ prolapse: a 12-yer study. Int Urogynecol J pelvic floor Dysfunct 2016;27(8):1201-1207 [↑](#endnote-ref-19)
20. Dessie SG, Armstrong K, Modest AM, Hacker MR, Hota LS: Effect of vaginal estrogen on pessary use. Int Urogynecol J 2016; 27:1423-1429 [↑](#endnote-ref-20)
21. Foxman B: Epidemiology of Urinary Tract Infections: Incidence, Morbidity and Economic Costs. Am J Mewd 2002;113(1A):5s-13s [↑](#endnote-ref-21)