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Safety and Efficacy of Cannabidiol-coated Tampons for Primary Dysmenorrhea: From Pre-Clinical Data to Post-Market Surveillance

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Title: Safety and Efficacy of Cannabidiol-coated Tampons for Primary Dysmenorrhea: From Pre-Clinical Data to Post-Market Surveillance

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Abstract
Primary dysmenorrhea affects an estimated 73% of people who menstruate worldwide. This high global prevalence underscores the need for effective strategies to address the substantial burden of menstrual pain. Despite this, current treatment options remain limited. Cannabidiol (CBD) treatments have been proposed for managing primary dysmenorrhea; however, their safety and efficacy remain largely unstudied. This two-part study presents a comprehensive evaluation of the safety and efficacy of CBD-coated tampons. The first part focuses on preclinical assessments, including irritation, toxic shock syndrome risk, acute systemic toxicity, skin sensitisation, vaginal irritation, and material-mediated pyrogenicity. The second part combines post-market surveillance data, including clinical complications collected from 2019-2024, and survey data collected from 2022-2024, including Manonski pain scores for rating menstrual pain severity prior to and during CBD tampon use. In preclinical assessments, all safety benchmarks were met. A total of 148 clinical complications were reported in relation to CBD-coated tampon use, equating to a prevalence of 0.58% (148/25327, 95% Confidence interval [CI]:0.49 - 0.68%), below the predefined target of <1%. From 42,000 users who were sent the survey, we received 2,123 responses from CBD-coated tampon users. Before CBD tampon use, the average self-reported Mankoski Pain Score was 6.35 (95% CI: 6.27–6.43, SD = 1.83). During use, mean scores were 3.78 (95% CI: 3.69–3.87, SD = 2.13), representing a mean reduction of 2.57 (95% CI: 2.45–2.69). These findings, corroborated by results from a previously published randomized controlled trial, provide complementary evidence that CBD-coated tampons may offer a safe and effective option for menstrual pain management. Future, large randomised control trials should explore optimum patterns of use of CBD-coated tampons.

Key words
Menstrual pain, primary dysmenorrhea, Cannabidiol, CBD

Abbreviations
3HTdR – Tritiated Methyl Thymidine
α-HCA / HCA – α-Hexylcinnamaldehyde
ANOVA – Analysis of Variance
bw – Body Weight
CBD – Cannabidiol

CFU – Colony-Forming Units
CI – Confidence Interval
DMF – N,N-Dimethylformamide
DEs – Dermal Equivalents
ELISA – Enzyme-Linked Immunosorbent Assay
EU – Endotoxin Equivalent Units
FDA – United States Food and Drug Administration
GMP – Good Manufacturing Practice
GOTS – Global Organic Textile Standard
H&E – Haematoxylin and Eosin
IACUC – Institutional Animal Care and Use Committee
ID – Identification Number
IL-1β – Interleukin-1 Beta
IP – Intraperitoneal
ISO – International Organization for Standardization
IV – Intravenous
LDPE – Low-Density Polyethylene
LLNA – Local Lymph Node Assay
LOD – Limit of Detection
MAT – Monocyte Activation Test
MVD – Maximum Valid Dilution
NATSAL – National Survey of Sexual Attitudes and Lifestyles
OECD – Organisation for Economic Co-operation and Development
PCOS – Polycystic Ovary Syndrome
Q4 – Fourth Quarter
RCT – Randomised Controlled Trial
RH – Relative Humidity
RPMI – Roswell Park Memorial Institute
s.d. – Standard Deviation
SEM – Standard Error of the Mean
TSS – Toxic Shock Syndrome
TSB – Tryptone Soya Broth
TSST-1 – Toxic Shock Syndrome Toxin-1

Main article

1. Introduction

Dysmenorrhea, or painful menstruation resulting from uterine cramps, is the most frequently reported gynaecological issue among menstruating individuals[1]. Dysmenorrhea can be classified into two types based on its underlying mechanisms [2,3]. Primary dysmenorrhea involves menstrual pain without any identifiable pelvic abnormality and typically occurs just before or during menstruation. In contrast, secondary dysmenorrhea arises from specific pathological conditions, including endometriosis, adenomyosis, leiomyomas, and pelvic inflammatory disease.

A recent systematic review and meta-analysis estimated the world prevalence of primary dysmenorrhea to be 73% (95% CI 68%-78%)[4]. This high prevalence is particularly concerning, considering primary dysmenorrhea can have significant impacts for wellbeing and quality of life[5–8]. In cases of severe or debilitating pain, it is linked to restrictions in physical and daily activities and may adversely affect mental health, academic achievement and occupational productivity[9–12].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the current first-line treatment for primary dysmenorrhea[12]. If NSAIDs are insufficient or contraindicated, hormonal therapies (for example combined contraceptives, progestin-only methods, or the levonorgestrel intrauterine device) offer substantial benefit by suppressing ovulation, thinning the endometrium, and decreasing prostaglandin production[12]. However, these first-line pharmacological options may not be suitable, effective or acceptable for all. For example, NSAIDs may be unsuitable for those with allergies or with certain kidney or heart conditions, and may also have side effects that are unacceptable, i.e. gastrointestinal impacts[13,14]. Research has been recommended to further evaluate efficacy of possible treatments[12].

Cannabidiol (CBD) has shown promise for pain management in various conditions[15–23]. Historically, cannabinoids have been used by women to alleviate menstrual pain[24]. More recent survey studies have reported how cannabinoid use significantly reduced pain and cramping, and improved quality of life, in participants with premenstrual syndrome, premenstrual dysphoric disorder and endometriosis[25,26]. There is some evidence suggesting that vaginal administration may be an effective route for cannabinoid-based treatments for menstrual pain[27,28]. Indeed, it has been suggested that CBD-coated tampons might be of value in managing dysmenorrhea, where the tampon device serves a dual function - vaginal delivery of a CBD-based formulation and absorption of menstrual fluids[27].

Tampons are an established medical device for the absorption of menstrual fluids during menstruation, with studies assessing their safety dating back to the 1940s[29]. Since then, new tampon compositions or designs undergo safety and efficacy assessments[30]. This is particularly important, as risk of Toxic Shock Syndrome (TSS), a rare but serious and potentially fatal illness, increases with tampon use, as well as with use of other vaginally inserted products, such as menstrual cups or diaphragms[31–33]. We aimed to evaluate the safety and efficacy of CBD-coated tampons for primary dysmenorrhea.

2. Materials and methods

2.1. Device

CBD-coated tampons (Daye™) are made from organic cotton certified by the Global Organic Textile Standard (GOTS), a voluntary sustainability benchmark that covers environmental protection, human rights, social criteria, and responsible business conduct across the post-harvest textile supply chain[34]. Each tampon contains 100 mg of *Cannabis sativa* hemp extract with 30% active CBD. These are evenly coated using automated C2-series coating machines (EQ06/EQ25) in a tightly controlled, GMP-compliant workflow conducted entirely within a cleanroom environment. Coated tampons are then dried and individually wrapped using validated equipment (EQ28) with metal detection to ensure integrity and sterility. Representative batches are periodically tested under separate quality control procedures for CBD content, microbiological safety, and biocompatibility to ensure ongoing process validation and product consistency. Tampon applicators are made from bio-based low-density polyethylene (LDPE).

2.2. Study design

This two-part study provides a comprehensive evaluation of CBD-coated tampons for primary dysmenorrhea. In the first part, we report preclinical safety assessments, including irritation, TSS risk, skin sensitisation, systemic toxicity, and material-mediated pyrogenicity. We then report post-market surveillance data from commercial use, reporting both clinical outcome and survey data, collected in line with ISO13485 and GMP requirements. These studies form part of a comprehensive programme of research, where pre-clinical assessments informed an already published randomised control trial (RCT)[27](see figure 1).

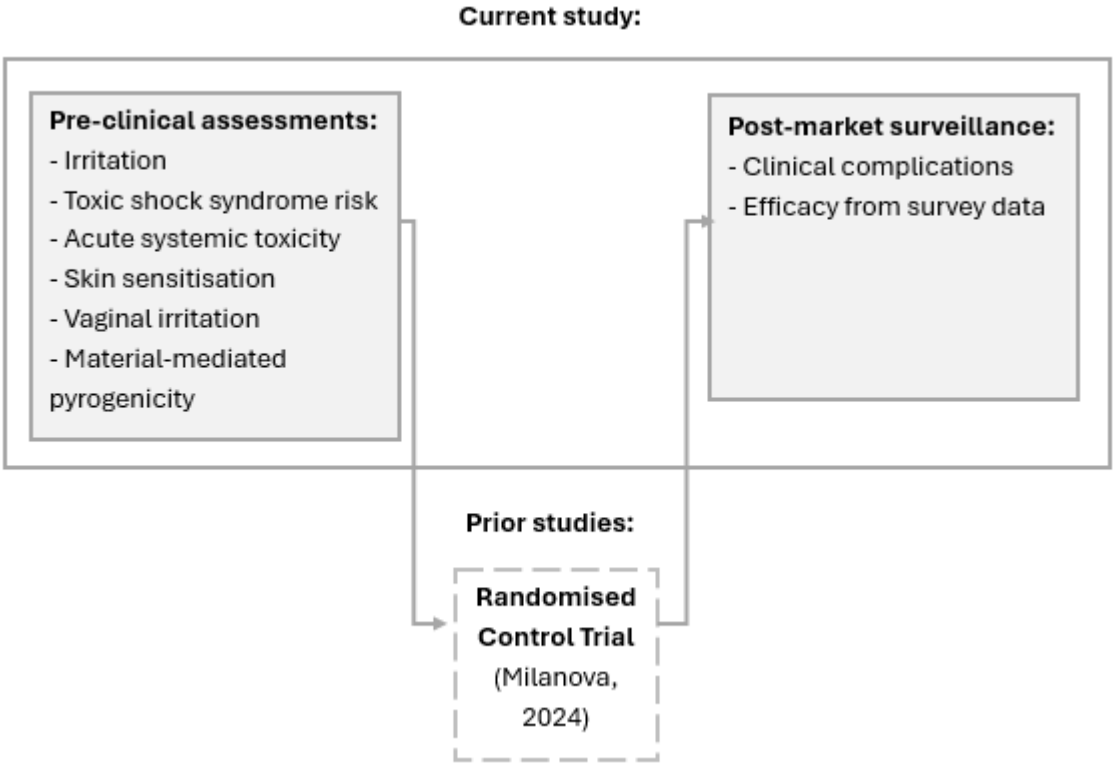

Figure 1. Programme of research into CBD-coated tampon safety and efficacy, depicting current study design and prior already published work.

Preclinical safety assessments were carried out according to the International Organization for Standardization (ISO) guideline 10993, which outlines standards for evaluating the biocompatibility of medical devices. The assessments were performed on CBD-coated tampons (Daye™) and were designed in accordance with relevant United States' Food and Drug Administration (FDA) Guidance for Industry 510(k) submissions[35]. Post-market surveillance is a regulatory requirement for gathering performance and safety data for medical devices, mandated by the FDA (21 CFR 820.198) and MDR (EU 2017/745).

2.3. Preclinical safety assessments

2.3.1. Irritation with colonised artificial skin model

To assess the antimicrobial and anti-inflammatory effects of the CBD-coated tampons, an artificial vaginal microbial consortium was established on Labskin, a synthetic 3D human skin model enabling realistic testing of antimicrobial and inflammatory responses. Two test items were evaluated: the CBD-coated tampon (Daye™) and a GOTS certified organic cotton tampon with cardboard applicator (from a different brand). An untreated Labskin model was used as a control. All groups consisted of three replicates (N=3).

Labskin was prepared by generating dermal equivalents (DEs) from primary adult human dermal fibroblasts embedded in a fibrin matrix. These were cultured under liquid with primary neonatal human keratinocytes for 48 hours. The Labskin was cultured at the air liquid interface until a stratified epidermis was formed, with incubation conditions for all cultures been 37°C in 5% (v/v) CO_2 at >95% RH. Lactobacillus acidophilus NCTC 4504 was cultured at 37°C, 5% CO_2 for 18–24 hours using deMann-Rogosa-Sharpe Agar. Using inoculation buffer GS25, a bacterial suspension (~1.1 × 10^6 CFU/mL) was prepared. Labskin units were colonized with ~10^4 CFU/cm² of L. acidophilus by applying 10 µL of the prepared inoculum. On the same day, Staphylococcus aureus ATCC 25923 and Candida albicans ATCC 90028 were cultured on Mueller-Hinton agar (37°C) and Sabouraud Dextrose agar (30°C), respectively, under aerobic conditions for 18–24 hours. Overnight cultures of S. aureus and C. albicans were used to prepare a mixed suspension in GS25 buffer (~1.1 × 10^4 CFU/mL). Labskin pre-colonised with L. acidophilus (~10^4 CFU/cm²) was then infected with 10^2 CFU/cm² of each pathogen. The colonised Labskin was incubated at 37°C, 5% CO_2, and >95% RH for ~2 hours until the surface was completely dry.

Disks approximately 3 mm in thickness were excised from the test tampons. These were placed on top of the colonised Labskin and incubated at 37°C, 5% CO_2, and >95% RH for 24 hours. After 24 hours, two 5 mm biopsy samples were aseptically removed from each infected wound and viable microbial numbers assayed by recovery on appropriate culture media. Three solid media were used: Mueller-Hinton agar supplemented with amphotericin B allowed the growth of S. aureus, deMann-Rogosa-Sharpe agar supplemented with amphotericin B allowed the growth of L. acidophilus, while Sabouraud dextrose agar supplemented with antibiotics allowed the growth of C. albicans. The remaining tissue from each biopsied Labskin was fixed in 10% neutral buffered formalin, processed, paraffin embedded, sectioned, and stained with H&E. Pro-inflammatory cytokines IL-1α and IL-23 released to the maintenance medium were assessed by ELISA (Human IL-1 α /IL-1F1 Quantikine®, Human IL-23 Quantikine®, R&D systems).

Statistical analysis was carried out to compare bacterial populations between samples. Normality of the data sets was tested using the Shapiro-Wilks test. Then, a non-parametric Kruskal-Wallis one-way analysis was performed to determine whether the samples for S. aureus originated from the same distribution, and a parametric one-way ANOVA was performed.

2.3.2. Toxic Shock Syndrome (TSS) risk and effect on vaginal microflora

To evaluate the effect of a CBD-coated tampon on vaginal microflora and transient pathogens, an in vitro study assessed growth and virulence of Lactobacillus species, E. coli, C. albicans, and S. aureus, including the morphogenetic switch of C. albicans and the release of toxic shock syndrome toxin-1 (TSST-1) by S. aureus. The study compared Daye's CBD-coated tampons against a GOTS certified organic cotton tampon with cardboard applicator (different brand). All groups had three replicates (N=3).

The study followed the protocols outlined in Section 9 (Preclinical Microbiology) of the US FDA Guidance for Industry 510(k)s to assess the effect of the test items on the growth of S. aureus, production of TSST-1 by S. aureus NCTC 11963, and growth of normal vaginal microflora species (Lactobacillus acidophilus NCTC 4504, Escherichia coli ATCC 25922, and Candida albicans ATCC 90028).

The procedure for testing samples mixed with a small portion of each test material in the presence of Staphylococcus aureus NCTC 11963 (inoculated at ~ 10^6 CFU/mL) was carried out using an 18 amino acid defined growth medium. Growth by viable count and medium pH was monitored at regular intervals throughout the growth cycle and compared to a control culture (no test material). Samples were taken at regular intervals for assay of Toxic Shock Syndrome Toxin-1 (TSST-1) by ELISA.

The assessment of Lactobacillus acidophilus NCTC 4504 in deMann Rogosa Sharpe Broth (Inoculated at ~ 10^6 CFU/mL) was by viable counting and medium pH in the presence of a small portion of each test material and compared to a control culture (no test material). The assessment of Escherichia coli ATCC 25922 in Tryptone Soya Broth (Inoculated at ~ 10^6 cfu/mL) was by viable counting and medium pH in the presence of a small portion of each test material and compared to a control culture (no test material). The assessment of Candida albicans ATCC 90028 in Tryptone Soya Broth (Inoculated at ~ 10^6 CFU/mL) was by viable counting, medium pH and cell morphology in the presence of a small portion of each test material and compared to a control culture (no test material).

Statistical analysis was performed using the Shapiro-Wilk test for normality assessment ($\alpha = 0.05$) on all bacterial and fungal growth data. For datasets that failed the normality test, the Wilcoxon matched-pairs signed rank test ($\alpha = 0.05$) was applied to compare differences between Daye, other brand, and control groups

2.3.3. Acute Systemic Toxicity in Mice

To assess the systemic response to CBD-coated tampons, a preclinical study was conducted in Crl:NMRI mice using both a polar extract (physiological saline) and a non-polar extract (sesame oil) of the test item, administered via intravenous (IV) or intraperitoneal (IP) injection.

The study followed regulatory guidelines (ISO 10993-11:2017: Biological evaluation of medical devices - Part 11: Tests for systemic toxicity), using the minimum number of animals required, as no acceptable non-animal alternative method was available.

The test item was dosed in the form of two extracts by single injection in the test group. Physiological saline solution extract was administered by intravenous injection (IV injection) and sesame oil extract was administered by intraperitoneal injection (IP injection) at a dose volume of 50 mL/kg bw. Animals treated with incubated extraction medium (saline or sesame oil) served as control (control groups). Five animals were included in each group, as detailed in Table 1, which lists the test groups, routes, and doses administered.

Table 1 - Groups of animals with the type of extract and route administered, Acute Systemic Toxicity in Mice study

Group Number	Description	Route	Dose Volume	Number of Females
1	Saline Vehicle Control	Intravenous	50 mL/kg bw	5
2	Saline Extract	Intravenous	50 mL/kg bw	5
3	Sesame Oil Vehicle	Intraperitoneal	50 mL/kg bw	5
4	Sesame Oil Extract	Intraperitoneal	50 mL/kg bw	5

Animals were assessed for any notable systemic clinical signs. The animals went under macroscopic examination after termination.

2.3.4. Skin Sensitisation in mice

Skin sensitisation potential of CBD-coated tampon was determined following dermal exposure by the ISO 10993 guideline method.

Two 0.1 g/mL extracts of the test item, CBD-coated tampon, were prepared with the extraction vehicles N,N-dimethylformamide (DMF) and 1% aqueous Pluronic PE9200 solution (1% Pluronic), respectively. Both extracts were prepared in compliance with Part 12 of the ISO 10993 standard. These extracts were tested for skin sensitization potential by local lymph node assay. The study was performed with vertebrate animals as no full regulatory in vitro alternative is available.

No preliminary irritation/toxicity test was performed. The extracts were tested without dilution. The main study was performed with the single maximum concentration from each test item extract: 100% (undiluted) extract in 1% Pluronic and 100% (undiluted) extract in DMF.

In the main assay, 25 female CBA/CaCrl mice were allocated to 5 groups of 5 animals each: One group received CBD-coated tampon extract in 1% Pluronic (100% [undiluted] final concentration), 1 group received CBD-coated tampon extract in DMF (100% [undiluted] final concentration), 2 negative control groups received the incubated vehicles (1% Pluronic or DMF), and the positive control group received 25 % (w/v) α-hexylcinnamaldehyde (HCA; in incubated extractant DMF).

The test item extracts were applied on the dorsal surface of ears of the experimental animals (25 µL/ear) for 3 consecutive days (days 1, 2, and 3). There was no treatment on days 4, 5, and 6. The cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine (3HTdR), and the values obtained were used to calculate stimulation indices (SIs).

2.3.5. Vaginal Irritation in Rabbit

To evaluate the vaginal irritation potential of CBD-coated cotton tampon extracts, the study was conducted in female New Zealand White rabbits in accordance with ISO 10993-10:2010 and ISO 10993-12:2012 guidelines. The study was approved by Charles River Laboratories Hungary's IACUC and conducted under GLP (OECD/ISO 10993).

The test item was extracted in physiological saline (polar) and sesame oil (non-polar) at a ratio of 0.1 g/mL, accounting for the tampon's absorbency (2 mL saline/g, 3.2 mL sesame oil/g). Extracts were incubated at 37°C for 72 hours. Twelve young adult female rabbits (9 weeks old, 2426–2716 g) were acclimated for 11 days and divided into four groups (n=3/group): saline control, sesame oil control, saline extract, and sesame oil extract. Each animal received 1 mL of the assigned extract intravaginally daily for five consecutive days.

Clinical observations for erythema, edema, discharge, and swelling were scored pre-dose, 1-hour post-dose, and 24 hours after the final dose using ISO 10993-10:2010 criteria. Post-mortem histopathology assessed epithelial integrity, leukocyte infiltration, vascular congestion, and edema in cervical, central, and caudal vaginal tissues.

Irritation indices were calculated per ISO 10993-10:2010 by subtracting the control group's average histopathological score from the test group's average. Descriptive statistics (mean ± SEM) were used for group comparisons. Due to the ISO-mandated sample size (n=3/group), inferential statistical tests (e.g., t-tests) were not performed, as the study relied on predefined irritation index thresholds for classification: 0 (non-irritant), 1–4 (minimal), 5–8 (mild), 9–11 (moderate), 12–16 (severe).

2.3.6. Material Mediated Pyrogenicity

To evaluate material-mediated pyrogenicity, the Monocyte Activation Test (MAT) and Test for Interfering Factors (EP 2.6.30) were performed on a tampon extract (AND-ASD-19-001). The test was conducted on three independent occasions using a single extraction process.

A commercially available kit (IL-1 BETA HUMAN ELISA, Invitrogen) using cryopreserved human blood as the monocyte source was used. The blood was incubated overnight with the sample to be tested. If pyrogenic substances were present in the tested sample, inflammatory cytokines such as IL-1β would be released. Culture supernatants were transferred to the pre coated microtiter plate with specific antibodies for IL-1β. After washing away any unbound substances, enzyme-linked polyclonal antibodies specific for IL-1β were added. The excess of the antibody-enzyme complex was removed by an additional washing step. IL-1β bound complex is then detected in a colour reaction started by the addition of substrate. The amount of colour produced is relative to the amount of IL-1β produced. Test sample results were interpolated from an endotoxin standard curve. Results were expressed as endotoxin

equivalent units (EU)/mL. The limit of detection (LOD) for this method and used in the calculation of maximum valid dilution was 0.25 EU/mL.

One sample (CBD-coated tampon) was tested using 1 extraction process, identified in the study AND-ASD-19-001. Sample supernatant was tested on 3 independent occasions at 3 different dilutions. The test for interfering factors consisted of testing the samples in the absence and presence of 0.5 EU/mL endotoxin (at or near the midpoint of the standard curve). The percentage recovery was calculated using the following formula: *Percentage recovery (%) = (Spiked Sample − Unspiked Sample) / Spike Control × 100%*. For a result to be accepted, the spike percentage recovery had to be between 50% and 200%.

To test for interfering factors, one sample of CBD-coated cotton tampon (S1, batch: 1001) was placed in a depyrogenated vial, submerged in 32 mL of RPMI, and incubated for 1 hour ± 5 minutes at 37°C ± 1°C. After incubation, the test sample piece was removed from the RPMI and the sample extract was used for further testing. Sample extract was tested at the following dilutions: undiluted, 1:2, and 1:2.5 (up to the maximum valid dilution [MVD] assigned to the product). Testing was conducted on 3 occasions by a single operator.

2.4. Post-Market Surveillance studies

2.4.1. Clinical complications

Customer-reported clinical complications were systematically collected and analysed as part of ongoing post-market surveillance of commercially available CBD-coated tampons, to further understand safety profile. Data were gathered from users in the United Kingdom and Europe between September 2019 and July 2025. As a regulatory requirement, this did not require ethical approval.

Prevalence of clinical complications was calculated using customer-reported clinical reactions or complications as the numerator, and the total number of CBD tampons sold as the denominator. Reported outcomes were recorded as free-text descriptions and systematically assigned to one of nine predefined categories (vaginal irritation / discomfort, allergic reaction, infection, pain or cramping, gastrointestinal symptoms, neurological / systemic symptoms, menstrual changes, tampon usage issues, other / unspecified). Each reported outcome was assigned a severity score based on the predefined Product Harms List and Risk Management Procedures, in line with ISO 14971:2019 Application of risk management to medical devices (Table 2).

Table 2. Severity of harm and classification target of CBD-tampon related clinical complications.

Code	**Severity**	**User**	**Target (% of total CBD-tampon users)**
1	Negligible	N/A	Occurs in <1% of users
2	Low	Inconvenience to patient: e.g. Tampon Leakage	Occurs in <1% of users

Code	Severity	User	Target (% of total CBD-tampon users)
3	Moderate	Injury requiring medical attention, but without long-term effects on user health, e.g. soft tissue damage No long-term effects on patient health	Occurs in <0.1% of users
4	High	Injury causing long-term/permanent damage.	Occurs in <0.0001% of users
5	Catastrophic	Results in death	Never

Reports were anonymised and assessed to determine the appropriate response according to the severity classification target. Data collection, classification, and response procedures followed standardised protocols to ensure consistency and regulatory compliance.

2.4.2. Survey

As part of Daye's post-market surveillance program, an observational survey was conducted in routine use settings to further evaluate the effectiveness and user experience of CBD-coated tampons. Ethical approval for the study was obtained from the Reading Independent Ethics Committee in July 2022.

The survey was distributed via email using Klaviyo during Q4 2022, Q2 and Q4 2023, and Q4 2024 to all active and non-active subscribers, namely individuals who had previously purchased and used Daye tampons. The questionnaire was hosted on Typeform, and informed consent was obtained prior to completion of the survey. A financial incentive was offered for survey completion.

The survey included structured items assessing self-reported pain scores (Mankoski Pain Scale, in line with previous publication[27]), side effects, and user satisfaction (Supplementary material 1). Response metrics, including participation and completion rates, were recorded via Typeform. To protect confidentiality, each respondent was given a unique anonymous ID for each survey period. These IDs were not connected across different periods, so we could not track the same individuals over time. As a result, analyses were based on all responses in the evaluation period, rather than on individual participants.

Data were summarised using descriptive statistics, and distributions for active and non-active users were compared to explore potential patterns associated with subscription discontinuation. Pain reduction was measured as the difference between self-reported pain scores before and during tampon use. For pain-score outcomes specifically, group differences by diagnosis, timing of tampon use, and quantity used were examined using one-way ANOVA, with post-hoc Dunnett or Tukey tests applied where applicable.

3. Results

3.1. Pre-Clinical studies

3.1.1. Irritation with colonised artificial skin model

No viable C. albicans were detected on any Labskin samples exposed to either the CBD-coated tampons (Daye™) or the uncoated tampons from another brand, nor in the control samples without tampons. However, microscopic analysis revealed invasion of C. albicans into the Labskin only in samples exposed to the uncoated tampons (other brand), while no invasion was observed in those exposed to CBD-coated Daye tampons or in control samples (figure 2).

Quantitative analysis showed differences of more than one log (90% reduction) in total bacterial counts between some samples; however, these differences were not statistically significant ($p > 0.05$). IL-1α release into the medium was not detected in any sample, including those exposed to the uncoated tampons from other brands with microbial colonisation. This indicates that despite microbial invasion observed with uncoated tampons (other brand), there was no detectable skin damage or irritation based on IL-1α levels.

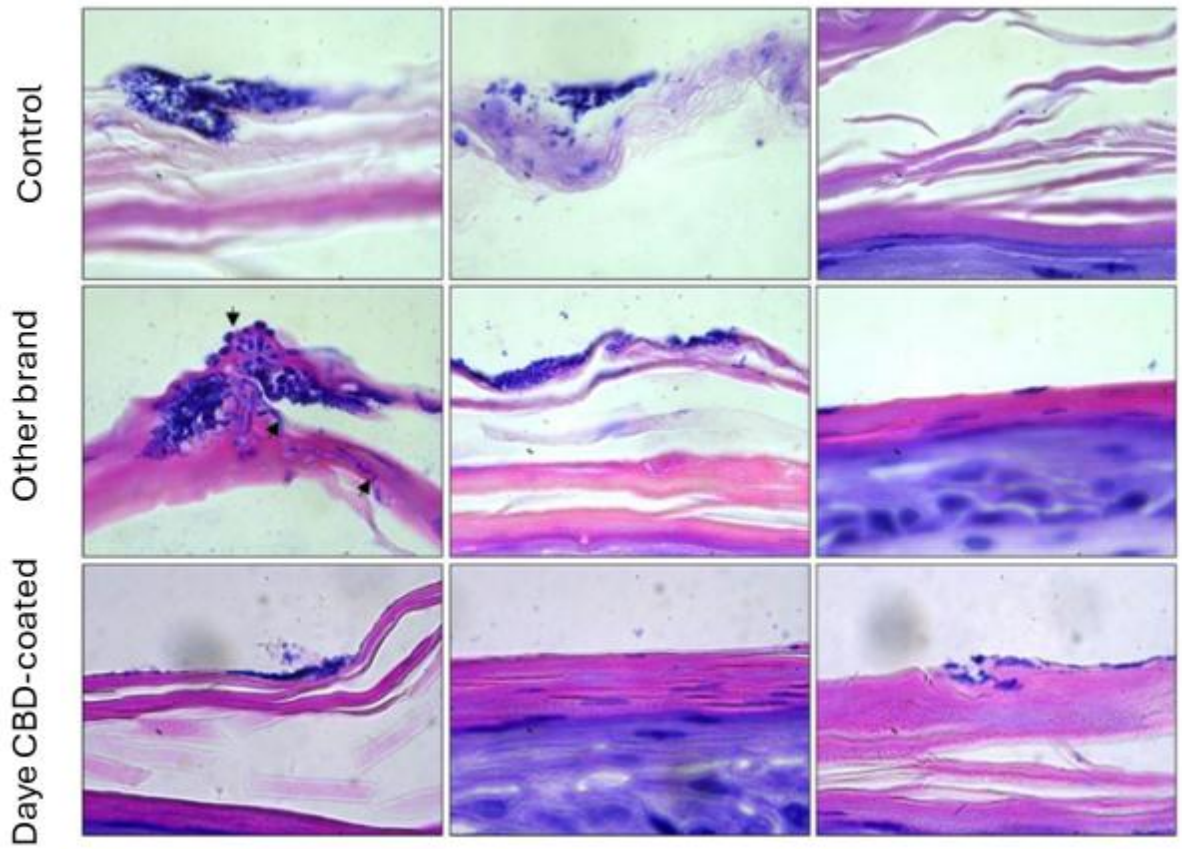

Figure 2 - C. albicans invading Labskin in the other organic tampon brand test sample (magnification 1000x)

3.1.2. Toxic Shock Syndrome (TSS) risk and effect on vaginal microflora

At the maximum recommended tampon wearing time of 8 hours, no detectable TSST-1 was present in any condition (Daye, other brand, or control). Following extended incubation to 24 hours, TSST-1 production diverged markedly between products. The Daye tampon yielded minimal toxin production at 0.33 ± 0.07 µg/mL, while the other brand tampon induced

substantially higher TSST-1 release at 3.22 ± 1.89 µg/m, representing approximately a tenfold difference (Figure 3).

Figure 3. TSST-1 toxin production in test cultures (mean values and standard deviation from 3 independent runs) at 24h time point.

S. aureus growth differences were not statistically significant; at 24 hours, Daye tampon increased growth by 0.22 LOG_{10} while other brand increased by 0.74 LOG_{10} compared to control. The Daye tampon increased pH by 0.12 units at 8 hours and 0.86 units at 24 hours, while other brand increased pH by 0.73 units at 24 hours only.

Daye tampon showed an initial negative effect on the beneficial vaginal microflora L. acidophilus, decreasing growth by 0.67 LOG_{10} at 8 hours, but this was reverted to a positive effect by 24 hours with an 0.83 LOG_{10} increase. In contrast, the other brand tampon consistently suppressed L. acidophilus growth at both timepoints (0.10 LOG_{10} at 8h; 0.44 LOG_{10} at 24h). The Daye tampon increased pH by 0.32 units at 8 hours, while the other brand did not alter pH throughout the experiment.

Daye tampon had a slightly positive effect on the other studied pathogens by decreasing the growth of both E. coli and C. albicans. Both Daye and other brand tampons reduced E. coli by >1 LOG_{10} at 2 hours (Daye: 1.42; other brand: 1.34). The Daye tampon maintained 0.13 LOG_{10} reduction at 8 hours, while other brand showed no difference at this timepoint. The Daye tampon showed minimal effects on C. albicans, with no change at 8 hours and 0.12 LOG_{10} reduction at 24 hours, while other brand reduced growth by 0.16 LOG_{10} at 8 hours and 0.21 LOG_{10} at 24 hours. Daye had no effect on hypha formation; other brand showed elevated hyphae (6.73%) at 24h incubation timepoint with concurrent contamination (Figure 4). Neither tampon affected pH of the medium. A bacillus-type bacterium contaminated the other brand tampons, confirmed by growth in sterile Tryptone Soya Broth. This contamination was only detected during the studies of growth of C. albicans, possibly because the other bacteria inhibited or outcompeted the contamination.

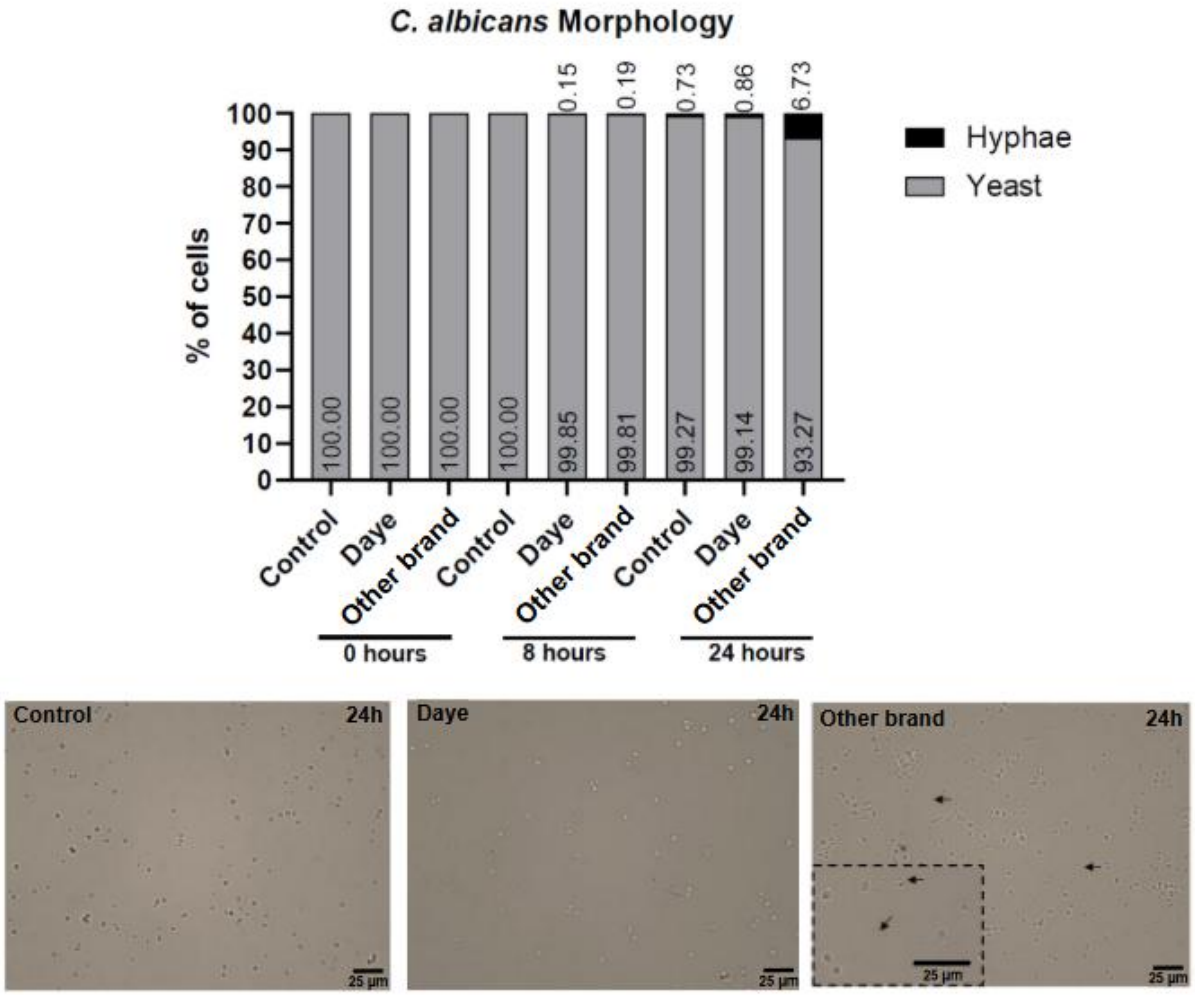

Figure 4 - Morphology of Candida albicans ATCC 90028 cells at 0, 8h and 24 hours of incubation in Tryptone Soya Broth at 34 oC with agitation. Quantification of C. albicans cells showing yeast or hypha form (top). Representative images used for hyphae/yeast quantification at 24 hours incubation (scale bar = 25 µm); arrows indicate bacterial contamination in the other organic tampon brand sample (bottom).

3.1.3. Acute Systemic Toxicity Study in Mice

The test item, a CBD-coated cotton tampon, administered via intravenous or intraperitoneal injection in the form of polar (saline) and non-polar (sesame oil) extracts, was considered to have no systemic toxicity under the conditions of this study (see table 3).

In IV treated animals with saline extract, no mortality or systemic clinical changes related to the test item extracts or vehicle control were observed. There was no effect on body weight

in any group during the study that could be related to the test item extract. There was no evidence of any gross macroscopic changes in the control or test group.

In IP treated animals with sesame oil extract, no mortality occurred. In 2 out of 5 animals in both groups (control and test group), swelling was observed around the injection site(s) from Day 1 to the last day of experiment Day 4, however this was considered to be procedure related with the large volume. Additional observation was activity decrease on the day of treatment in 1 out of 5 animals for a short time (only at 4-hour). Three out of 5 animals were symptom-free. There was no effect on body weight in any group during the study that could be related to the test item extract.

During the macroscopic observation in the skin, inguinal area (right or bilateral) clear or yellow liquid material was observed, subcutaneous in 4 out of 5 animals (both control and test groups). This observation is attributed to the procedure. There was no evidence of any gross macroscopic changes that could be attributed to the test item extract.

Table 3 - Acute Systemic Toxicity Study in Mice: Individual clinical observations

Treatment Group	Animal Number	Observation	Observation Days					Frequency
			1		2	3	4	
			30’	4h				
Saline Vehicle Control	9077	Symptom Free	+	+	+	+	+	5/5
	9078	Symptom Free	+	+	+	+	+	5/5
	9079	Symptom Free	+	+	+	+	+	5/5
	9080	Symptom Free	+	+	+	+	+	5/5
	9081	Symptom Free	+	+	+	+	+	5/5
Saline Extract	9082	Symptom Free	+	+	+	+	+	5/5
	9083	Symptom Free	+	+	+	+	+	5/5
	9084	Symptom Free	+	+	+	+	+	5/5
	9085	Symptom Free	+	+	+	+	+	5/5
	9086	Symptom Free	+	+	+	+	+	5/5
Sesame Oil Vehicle Control	9087	Symptom Free	+	+	+	+	+	5/5
	9088	Symptom Free	+	-	-	-	-	1/5
		Swelling right side (treatment area)	-	+	+	+	+	4/5
	9089	Symptom Free	+	+	+	+	+	5/5
	9090	Symptom Free	+	+	+	+	+	5/5
	9091	Symptom Free	+	-	-	-	-	1/5
		Swelling right side (treatment area)	-	+	+	+	+	4/5
Sesame Oil Extract	9092	Symptom Free	+	+	+	+	+	5/5
	9093	Symptom Free	+	+	+	+	+	5/5
	9094	Symptom Free	+	-	-	-	-	1/5
		Activity decrease	-	+	-	-	-	1/5
		Swelling right side (treatment area)	-	+	+	+	+	4/5
	9095	Symptom Free	+	-	-	-	-	1/5
		Swelling right side (treatment area)	-	+	+	+	+	4/5
	9096	Symptom Free	+	+	+	+	+	5/5

Remarks:
+ = present
- = absent
h = hour (s)

' = minute
Frequency of observation = number of occurrence of observation / total number of observations

3.1.4. Skin Sensitisation in mice

During the main study no mortality or signs of systemic toxicity were observed. No test item residue was observed on the ears of the animals. There were no indications of any irritancy at the site of application on the experimental animals. No evidence of test item related effect was observed on the mean body weight changes.

The stimulation index values were 0.6 for the DMF, and 1.2 for the 1% Pluronic test item extracts. The appearance of the lymph nodes was normal in the negative control groups and in all the test item extract treated dose groups. Larger than normal lymph nodes were observed in the positive control group. The result of the positive control substance A-Hexylcinnamaldehyde (HCA) dissolved in incubated DMF was used to demonstrate the appropriate performance of the assay. A lymphoproliferative response in line with historic positive control data was noted for the positive control chemical, this result confirmed the validity of the assay.

Under the conditions of the assay, CBD-coated tampon, tested as DMF and aquatic (1% Pluronic) extracts, was shown to have no sensitization potential (non sensitizer) in the local lymph node assay.

3.1.5. Vaginal Irritation in Rabbit

No mortality or systemic clinical signs were observed in any group. Body weights remained stable throughout the study. Clinical observations revealed no erythema, edema, swelling, or discharge in any group.

Histopathological evaluation showed that animals treated with the saline extract of the CBD-coated tampon exhibited mild epithelial cell degeneration, minimal-to-moderate leukocyte infiltration, and minimal-to-mild vascular congestion compared to controls. No edema was observed in either group. The irritation index for the saline extract was 2.00, classifying it as a "minimal irritant." In contrast, animals treated with the sesame oil extract showed no significant differences from controls in epithelial integrity, leukocyte infiltration, vascular congestion, or edema. The irritation index for the sesame oil extract was -0.34, classifying it as "non-irritant."

The CBD-coated tampon applied to the rabbit's vagina in the form of extracts was considered "minimal irritant" using saline extract and "non-irritant" using sesame oil extract according to the calculated ISO irritation index values.These findings suggest that the polar nature of saline enhances irritant interactions, while the non-polar nature of sesame oil limits them.

3.1.6. Material Mediated Pyrogenicity

The assay acceptance criteria were met in this study and are summarized in Table 4. The results of the test for interfering factors are summarised in Table 5. The values of the spike control are shown in Table 6.

Table 4 - AND-ASD-19-002 Assay Plates Acceptance Criteria met and summarised.

Assay Number	Assay Plate	LOD below 0.25 EU/mL (pass/fail)	Regression of responses statistically significant p<0.01 (pass/fail)	Standard curve does not deviate significantly from the theoretical curve (pass/fail)
AND-ASD-19-002_1	AND-1A	0.0887 (Pass)	P ≤ 0.0001 (Pass)	No evidence of inadequate model (Pass)
AND-ASD-19-002_2	AND-2A	0.1189 (Pass)	P ≤ 0.0001 (Pass)	No evidence of inadequate model (Pass)
AND-ASD-19-002_3	AND-3A	0.1246 (Pass)	P ≤ 0.0001 (Pass)	No evidence of inadequate model (Pass)

Table 5 - Test for interference factors: Summary results for endotoxin spike.

Assay Number	Sample	Dilution	Results (EU/mL)		Spike Control (EU/mL)	% Recovery
			Unspiked	Spiked		
AND-ASD-19-002_1	S1	Neat	0.0000[1]	0.4296	0.5325	80.7
		1:2	0.0000[1]	0.4348		81.7
		1:2:5	0.0000[1]	0.4669		87.7
AND-ASD-19-002_2	S1	Neat	0.0000[1]	0.5662	0.5893	96.1
		1:2	0.0000[1]	0.5993		101.7
		1:2:5	0.0000[1]	0.5740		97.4
AND-ASD-19-002_3	S1	Neat	0.0000[1]	0.6271	0.6413	97.8
		1:2	0.0000[1]	0.5505		85.8
		1:2:5	0.0000[1]	0.7777		121.3

[1]Values below the LOD of the assay (Limit of Detection = 0.25EU/mL) so “0” value was used to calculate the %recovery

Table 6 - Results of Spike Control - Endotoxin

Assay Number	Spike Control	Result (EU/mL)	Mean Results (EU/mL)	Standard Deviation	CV%[1]
AND-ASD-19-002_1	Endotoxin (0.5 EU/mL)	0.5043	0.5325	0.032	6.0
		0.5457			
		0.5087			
		0.5712			
AND-ASD-19-002_2	Endotoxin (0.5 EU/mL)	0.6300	0.5893	0.060	10.2
		0.6465			
		0.5646			
		0.5161			
	Endotoxin	0.9142[2]	0.6413	0.0506	7.9

AND-ASD-19-002_3	(0.5 EU/mL)	0.6433			
		0.5897			
		0.6908			

[1]CV% must be ≤20%
[2]Identified as a true outlier and removed from further calculations

Across all three occasions (AND-ASD-19-002_1, _2, and _3), CBD cotton tampon sample S1 (batch 1001) met the 50–200% acceptance criteria for endotoxin recovery across the neat, 1:2, and 1:2.5 dilutions. Recovery values ranged from 80.7% to 87.7% on occasion 1, 96.1% to 101.7% on occasion 2, and 85.8% to 121.3% on occasion 3.

For all unspiked dilutions of sample S1 across the three occasions, results were below the assay's limit of detection (<0.25 EU/mL).

The sample was therefore considered free of pyrogens under the tested conditions. No interfering factors were observed at any of the assessed dilutions (neat, 1:2, and 1:2.5). The MAT assay was deemed suitable for testing CBD cotton tampon samples extracted into RPMI at 37 °C ± 1 °C for 1 hour ± 5 minutes without shaking, for dilutions from neat up to 1:2.5.

3.2. Post-Market Surveillance studies

3.2.1. Clinical complications

Between September 2019 and July 2025, a total of 148 clinical complications or reactions were reported in relation to the use of Daye CBD-coated tampons, which equates to a prevalence of 0.58% (148/25327, 95% CI:0.49 - 0.68%). This is below the predefined target of <1% of users throughout the entire period.

Of the 148 reported clinical complications for CBD-coated tampons, 110 were classified as severity score 2, 22 as severity score 3, and 11 as severity 2/3 (see table 7). Five cases had unspecified severity. While most outcomes were mild, the severity score 3 cases involved more serious symptoms such as intense cramping, TSS-like effects, and suspected interactions with medication.

Table 7: Clinical complication severity and characteristics amongst all CBD tampon purchasers (n=25, 327)

	n (%)
Severity Score	
2	10 (0.04)
2/3	11 (0.04)
3	22 (0.09)
Unspecified	5 (0.01)
Characteristics	
Allergic reaction	15 (0.06)

Gastrointestinal Symptoms	15 (0.06)
Infection	39 (0.15)
Menstrual changes	6 (0.02)
Neurological/systemic symptoms	17 (0.07)
Pain or cramping	14 (0.06)
Tampon usage issues	2 (0.01)
Vaginal irritation or discomfort	24 (0.09)
Other or unspecified	16 (0.06)

3.2.2. User survey

Between Q4 2022 and Q4 2024, we sent the survey to 42,000 users who had consented to contact, and we received 2,465 (5.9%) responses (see figure 5). Of the 2,465 responses, 2,123 (86.1%) indicated use of CBD-coated tampons, while 342 (13.9%) indicated exclusive use of non-coated tampons. Of the 2123 responses from CBD-tampon users, 1210 (57%) were active users, and 913 (47% were non-active users).

Figure 5. Participant flowchart for the post-market surveillance survey

Of 1210 active users who responded, 74.0% (896) were asked about their gynaecological history with 78.9% (707/896) reported no gynaecological conditions or diagnoses and 6.7% (60/896) reported a diagnosis of endometriosis and 6.1% (55/1210) polycystic ovarian syndrome (PCOS) (Table 8).

Table 8: Gynaecological history of active (n=896) and non-active (n=407) CBD tampon users who responded to the survey and were asked about gynaecological conditions.

	Active users (n=1210), n (%)	Non-active users (n=913), n (%)
Gynaecological history		
None reported	707 (78.9)	407 (75.7)
Endometriosis	60 (6.7)	49 (9.1)
Polycystic ovarian syndrome	55 (6.1)	43 (8.0)

Fibroids	19 (2.1)	5 (1.2)
Adenomyosis	14 (1.6)	11 (2.0)
Primary dysmenorrhea	5 (0.6)	1 (0.2)
Pelvic inflammatory disease	3 (0.3)	2 (0.4)
Other	33 (3.7)	20 (4.9)

Almost half of active CBD tampon users (48.5%, 587/1210) used 5-10 CBD tampons per month (see table 9). Just over one fifth of active participants (20.4%, 247/1210) used CBD tampons throughout their entire cycle. A greater proportion of participants used CBD tampons only during the first (13.8%, 167/1210), second (30.1%, 375/1210) or third (20.7%, 250/1210) days of their period. Most people experienced pain relief fairly quickly, with 435/1,209 (36.0%) reporting relief within 30 minutes and a total of 671/1,209 (55.5%) within 45 minutes, though a sizable minority had missing data (278/1,209, 23.0%), which limits precise interpretation.

Table 9: Patterns of CBD-coated tampon use and pain relief amongst active (n=1210) and non active (n=913) CBD tampon users who responded to the survey.

	Active users (n=1210), n (%)	Non-active users (n=913), , n (%)
Monthly CBD tampon usage		
Fewer than 5 per month	346 (28.6)	368 (40.3)
5-10 per month	587 (48.5)	406 (44.5)
10-20 per month	260 (21.5)	125 (13.7)
More than 20 per month	17 (1.4)	14 (1.5)
Pattern of use of CBD-coated tampon during period		
During entire period	247 (20.4)	141 (15.4)
First day of period	167 (13.8)	153 (16.8)
First two days of period	375 (30.1)	292 (32.0)
First three days of period	250 (20.7)	153 (16.8)
Only when I start feeling cramps	148 (12.2)	153 (16.8)
Never	-	1 (0.1)
Missing	23 (1.9)	18 (2.0)
Onset of pain relief		
Almost immediately	37 (3.1)	25 (2.7)

Within 15 minutes	199 (16.4)	122 (13.4)
Within 30 minutes	435 (36.0)	285 (31.2)
Within 45 minutes	165 (13.6)	140 (15.3)
1 hour or more	96 (7.9)	93 (10.2)
Missing	278 (23.0)	248 (27.2)
Duration of pain relief		
Less than 30 minutes	15 (1.2)	7 (0.8)
1-2 hours	264 (21.8)	182 (19.9)
2-4 hours	473 (39.1)	362 (39.6)
4-6 hours	149 (12.3)	103 (11.3)
7+ hours	29 (2.4)	12 (1.3)
Missing	280 (23.1)	247 (27.1)

3.2.3. Efficacy of CBD-coated tampons at reducing pain amongst active and non-active users

Before tampon use, average self-reported Mankoski Pain score was 6.35 (95% CI: 6.27-6.43, s.d. 1.83). Comparing between active and inactive users, mean values of self-reported Mankoski Pain Scores were 6.40 (95% CI: 6.30 - 6.50 s.d.1.77) among active users and 6.30 (95% CI: 6.18- 6.42, s.d.=1.89) among non-active users, with no statistically significant difference between the groups (p=0.22). The distribution of pre-use scores was skewed toward the upper end of the scale, with the largest proportion of responses in the 7–8 range (Figure 6, A; accompanying table in supplementary material 2).

During use, mean scores were 3.78 (95% CI: 3.69-3.87, s.d. 2.13), a reduction of 2.57 (2.45-2.69). Comparing between groups, we saw 3.76 in both active (95% CI: 3.66-3.90, s.d. 2.12) and non active groups (95%CI: 3.61- 3.90, s.d.=2.2). The mean change in pain was 2.62 (95% CI:2.46-2.78) for active users and 2.54 (95% CI: 2.34-2.74) for non-active users, with no statistically significant difference between groups (p = 0.52). The distribution of scores during use shifted toward the 2–3 range (Figure 6, B).

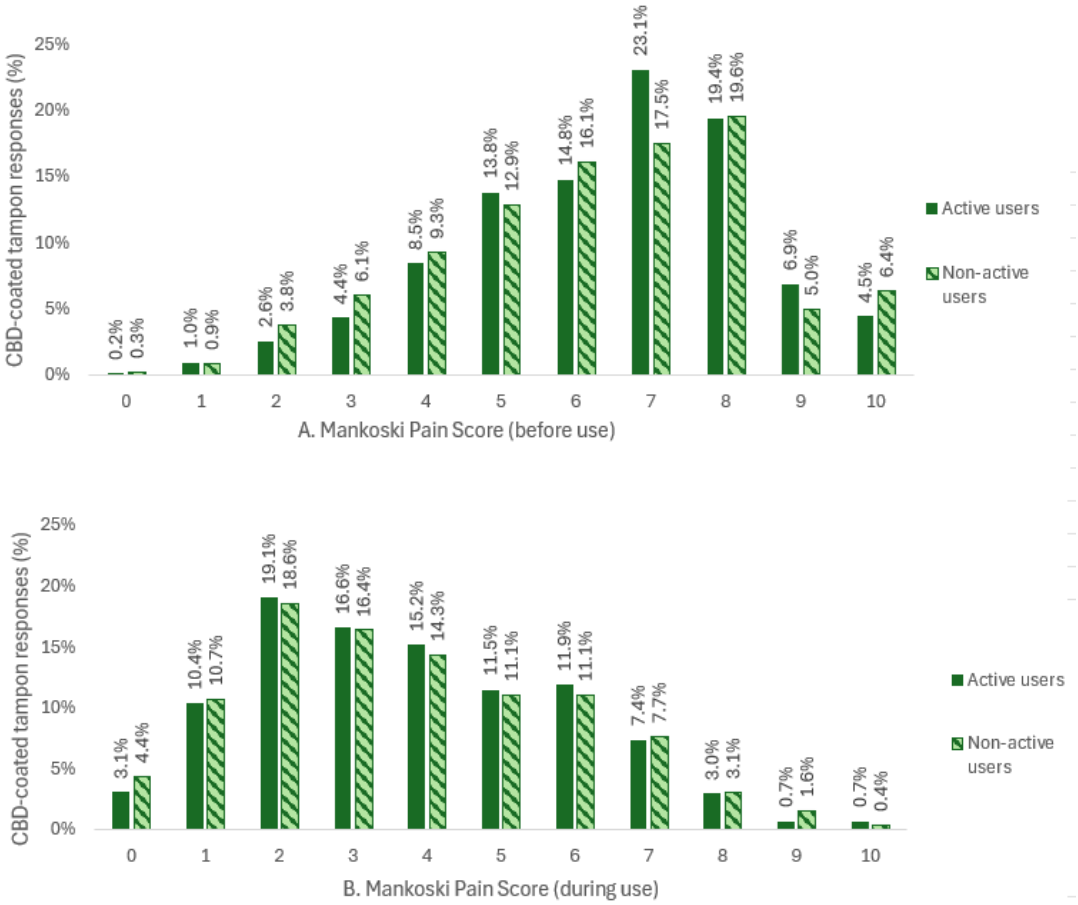

Figure 6. Distribution of self-reported Mankoski Pain Scores before (top, A) and during (bottom, B) CBD-coated tampon use, measured on the 0–10 Mankoski scale, where higher scores indicate greater pain severity. Data are shown for responses from active and non-active subscribers.

3.2.4. Patterns of tampon usage and pain scores

Statistical analyses examined differences in pain-score reduction by diagnosis, timing of tampon use, and quantity used (see table 10). We saw no significant difference in mean pain-score reduction between diagnosis groups ($F(6, 1427) = 0.55$, $p = 0.77$, $R^2 = 0.0023$). Post-hoc Dunnett's tests found no significant differences between the no-diagnosis group and any diagnosis group (all $p > 0.87$), indicating that the pain-relieving effect was consistent irrespective of gynaecological diagnosis. We did see a significant effect of tampon use timing ($F(4, 2042) = 10.46$, $p < 0.0001$, $R^2 = 0.0201$) and quantity ($F(3, 2084) = 33.37$, $p < 0.0001$, $R^2 = 0.0458$). on pain-score reduction.

Table 10: One-way ANOVA results for pain-score reduction by diagnosis, timing of tampon use, and quantity used amongst active and non active CBD tampon users (n=2123)

Predicator variable	n	$F(df_1, df_2)$	p-value	R^2
Diagnosis	1434	F(6, 1427) = 0.55	0.77	0.0023

Timing of tampon use	2047	F(4, 2042) = 10.46	< 0.0001	0.0201
Quantity of tampons used	2088	F(3, 2084) = 33.37	<0.0001	0.0458

Using Tukey post-hoc tests, we explored differences in mean pain score reductions by timing and quantity of tampons used (see table 11). Post-hoc (Tukey) tests showed that pain-score reduction was greater with tampon use throughout the cycle than on the first day ($p = 0.021$) or first two days ($p < 0.0001$), and was higher for three-day use ($p < 0.0001$) or use at cramps onset ($p = 0.031$) compared with two-day use. Mean pain-score reductions rose from 2.12 (<5 tampons) to 2.71 (5–10) and 3.15 (>10), but dropped to 2.16 for >20. Post-hoc (Tukey) tests found all increases significant except <5 vs. >20, with >10 greater than 5–10 ($p = 0.0001$) and >20 ($p = 0.0108$).

Table 11: Mean pain-score reduction by timing and quantity of tampon use, with post-hoc test results, amongst active and non active CBD tampon users

	Mean pain score reduction	Significant differences (Tukey post-hoc)
By timing of tampon use (n=2047)		
During entire period	2.90	Greater than first day ($p = 0.021$) and first two days ($p < 0.0001$)
First day of period	2.50	Lower than throughout cycle ($p = 0.021$)
First two days of period	2.28	Lower than throughout cycle ($p < 0.0001$), three-day use ($p < 0.0001$), and cramps onset ($p = 0.031$)
First three days of period	2.83	Greater than two-day use ($p < 0.0001$)
Only at onset of cramps	2.63	Greater than two-day use ($p = 0.031$)
By quantity of tampons used (n=2088)		
Fewer than 5 per month	2.12	Lower than 5–10 ($p < 0.0001$) and >10 ($p < 0.0001$); not different from >20 ($p = 0.0108$).
5-10 per month	2.71	Lower than >10 ($p = 0.0001$)
10-20 per month	3.15	Greater than 5–10 ($p = 0.0001$) and >20 ($p = 0.0108$)
More than 20 per month	2.16	Lower than >10 ($p = 0.0108$)

3.2.5. Side effects

When asked if they agreed with the statement “They [CBD tampons] have removed my menstrual pain entirely”, only 4.4% (53/1210) of active users agreed. However, 75.8% (917/1210) of active users agreed that “They have reduced my menstrual pain” (Table 12).

When presented with a list of both positive and negative side effects, and asked if they had ever experienced any when using the CBD Tampons, the majority of responses reported positive side effects. For example, pain relief was the most common benefit (79.1% of active users; 74.2% of non-active users), followed by reduced back pain (35.7% and 31.4%, respectively), reduced stress/anxiety (28.6% and 25.7%), better mood (27.4% and 27.3%), and better sleep (25.5% and 21.7%). Among responses indicating negative side effects, vaginal discomfort was reported in 4.2% of active-subscription responses and 4.1% of non-active-subscription responses, while vaginal itching was reported in 2.6% and 2.3%, respectively.

Table 12: Side effects reported amongst active and non active CBD tampon users responding to survey (n=2123)

	Active users (n=1210), n (%)	Non-active users (n=913), , n (%)
Agreement with statement:		
They have removed my menstrual pain entirely	53 (4.4)	59 (6.5)
They have reduced my menstrual pain	917 (75.8)	623 (68.2)
I use fewer pain-killers with the CBD tampon	767 (63.4)	524 (57.4)
I have fewer infections like thrush, yeast, UTIs or bacterial vaginosis (BV) after using the CBD tampon	221 (18.3)	122 (13.4)
I have noticed other physical benefits	145 (12.0)	84 (9.2)
Positive side effects		
Pain relief	957 (79.1)	677 (74.2)
Reduced stress/anxiety	346 (28.6)	235 (25.7)
Better sleep	308 (25.5)	198 (21.7)
Better mood	332 (27.4)	249 (27.3)
Better perceived quality of life	249 (20.6)	182 (19.9)
Better digestion, less bloating	111 (9.2)	90 (9.9)
Reduced back pain	432 (35.7)	287 (31.4)
Reduced headaches	156 (12.9)	88 (9.6)
Reduced vaginal infections (Eg. Thrush, abnormal discharge)	160 (13.2)	91 (10.0)
Reduced rate of UTI infections	79 (6.5)	50 (5.5)
Increased energy levels	55 (4.5)	49 (5.4)

Other positive side effects	70 (5.8)	61 (6.7)
Negative side effects		
Worsening cramps	11 (0.9)	8 (0.9)
Irritation	24 (2.0)	7 (0.8)
Allergic reaction	1 (0.1)	0 (0.0)
Thrush	9 (0.7)	9 (1.0)
Skin injury from the applicator	26 (2.1)	18 (2.0)
Vaginal itching	32 (2.6)	21 (2.3)
Vaginal discomfort	51 (4.2)	37 (4.1)
Vaginal swelling	4 (0.3)	1 (0.1)
Dizziness	11 (0.9)	8 (0.9)
Fever	1 (0.1)	0 (0.0)
Nausea	10 (0.8)	13 (1.4)
Abnormal discharge	5 (0.4)	2 (0.2)
None of the above (side effects)	1033 (85.4)	779 (85.3)
Other negative	33 (2.7)	28 (3.1)

4. Discussion

In this study, we report preclinical and post-market surveillance data on CBD-coated tampons, providing new insights into their safety and user-reported effectiveness. These findings build upon previously published RCT data[27]. By combining new preclinical safety assessments with real-world user experiences, this study offers a more comprehensive perspective on the potential of CBD-coated tampons for managing primary dysmenorrhea.

Our findings suggest the CBD-coated tampons are safe. Biocompatibility testing, including cytotoxicity, sensitization, vaginal irritation, and systemic toxicity studies, showed no significant adverse effects. Importantly, there was no increase in microbial populations observed in Labskin models, indicating that CBD-coated tampons do not disrupt the vaginal microbiota. Inflammatory markers associated with fever or immune response were not detected, and a reduced risk of toxic shock syndrome (TSS) was observed compared to control tampons. The FDA-required biocompatibility panel, including vaginal irritation, toxicity, skin sensitisation, and material-mediated pyrogenicity, met all regulatory standards. The vaginal irritation study confirmed that CBD-coated tampons did not alter vaginal physiology, and the skin sensitisation study showed no evidence of irritancy at the site of application. These findings collectively demonstrate product biocompatibility, which provided the foundation for our previously published RCT and the post-market surveillance study reported herein.

The very low prevalence of adverse events, as collected through regulated post-market surveillance clinical reactions and complications data, over a substantial period, further supports the safety of the CBD-coated tampon. This is also supported by the survey data, where, on the whole, positive side effects, in particular pain relief, were reported, and similarly low proportions of negative side effects were reported. For example, of active users, 2.0% reported irritation, 2.6% reported vaginal itching, 4.2% reported vaginal discomfort and 0.7% reported thrush. It is important to note that many of these conditions are prevalent in the general population. For example, NATSAL, a population level survey in the United Kingdom, estimated that almost one in three women between the age of 16-74 had been diagnosed with thrush in their lifetime[36].

Further exploring results from our post-market surveillance survey, mean pain scores decreased from approximately 6.4 before tampon use to 3.8 during use, representing a substantial reduction. Pain relief was similar among participants with and without previous gynaecological diagnoses, including endometriosis and PCOS, suggesting a benefit in pain reduction irrespective of underlying conditions, some of which are associated with secondary dysmenorrhea. In contrast, both the timing and quantity of tampon use were associated with degree of relief. Greater reductions in pain score were reported with more sustained use across the cycle and with moderate quantities of use (around 5–10 tampons), while effects plateaued or declined at very high use levels. A potential dose-dependent response, with increased suppository use associated with greater reduction of symptoms, was suggested in a similar study which explored use of a CBD vaginal suppository for menstrual-related pain and discomfort compared to a treatment-as-usual group[28].

Our findings align with and extend those of our previously published RCT, which showed statistically significant pain reduction with CBD tampons compared to placebo (n=63) (27). The mean reduction in pain, expressed as a percentage of baseline pain, was 69% versus 51% on day 2 of the first menstrual cycle (p = 0.05), 67% versus 49% on day 1 of the third cycle (p = 0.03), and 71% versus 47% on day 2 of the third cycle (p = 0.01). The RCT findings suggested that localised vaginal administration of cannabidiol may provide enhanced analgesic effects for primary dysmenorrhea, particularly during the initial days of menstruation when pain intensity is highest. In the present observational study, participants reported the largest reductions in pain when tampons were used throughout the menstrual cycle, with slightly smaller benefits when use was limited to the first or first two days. These differences likely reflect the distinction between controlled efficacy conditions and real-world use: while the RCT confirms that CBD tampons are effective during peak pain, sustained or anticipatory use in everyday settings may enhance overall pain relief. Together, these results suggest that both targeted and prolonged use may provide meaningful analgesic benefits. Larger RCTs are warranted to investigate optimal patterns of use[37].

This study should be interpreted considering limitations, in particular in design. Limitations of post-market surveillance studies include their reliance on self-reported data, which is inherently subject to recall bias and variability in individual experiences, and missing data. These biases are particularly relevant considering participants are being asked to recall pain, a complex, inherently subjective experience. Additionally, potential selection bias may exist among survey respondents, as those with particularly positive or negative experiences may be more likely to participate, or to respond to certain questions. To mitigate this, we collected and analysed data from those who no longer continued to be active CBD tampon users, and

found no difference in the reduction in pain score reported. We recognise that further RCTs with larger sample sizes and complete data are needed to confirm these findings and explore optimal dosing and chronic use effects Replicating genotoxicity and sub-chronic toxicity tests, as performed by Tennille K. Marx et al., using cannabinoids extracted from CBD-coated tampons, would provide further safety validation[38]. Additionally, reproductive studies assessing the impact of CBD tampons on fertility would be beneficial, considering limited existing research. From a clinical perspective, further investigations into the effectiveness of CBD tampons for endometriosis-related pain could offer valuable insights. Exploring the kinetics of CBD absorption through vaginal mucosa and conducting metabolomics studies to assess pain biomarkers in serum samples could enhance our understanding of CBD's mechanism of action in menstrual pain relief.

5. Conclusions

Our findings from preclinical studies and post-market surveillance data, combined with RCT evidence, support the safety and potential efficacy of CBD-coated tampons for managing primary dysmenorrhea. This alternative approach to first-line medications may offer a valuable option for individuals seeking menstrual pain relief. Further research is warranted to fully establish the long-term safety and efficacy of this intervention, in comparison to current first line treatments.

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Author contributions

EP led statistical analysis and manuscript writing. VM conceived of the study, data collection tools, contributed to interpretation and supported manuscript writing and editing. NT contributed to interpretation, reviewed and approved final manuscript for submission. DK contributed to interpretation, reviewed and approved final manuscript for submission. AM contributed to interpretation, reviewed and approved final manuscript for submission. HB contributed to interpretation, reviewed and approved final manuscript for submission.

Conflict of interests

The authors wish to declare competing financial and non-financial interests. EP reports a relationship with Anne's Day Ltd. that includes employment. NT reports a relationship with Anne's Day Ltd. that includes membership of the organisation's medical advisory board. DK reports a relationship with Anne's Day Ltd. as an equity holder and a member of its Scientific Advisory Board. HB reports a relationship with Anne's Day Ltd. that includes prior employment, equity, and membership of the organisation's medical advisory board. VM reports a relationship with Anne's Day Ltd. that includes employment and equity or stocks. VM also has patents transferred to Anne's Day Ltd. AM declares no financial or non-financial competing interests.

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Supplementary material

Supplementary material 1

Post-marketing surveillance questionnaire, December 2024

#	Qs	Answers	Logic
I	Before we get started, please take the time to read Daye's data consent statement.	- I accept - I don't accept	
1.	How many months have you been using Daye's tampons?	- Less than 1 month - 1-3 months - 3-6 months - 6-12 months - 12-18 months - More than 18 months	
2.	Do you agree with any of the following statements about the Daye tampons?	- The applicator is easy to use and convenient - I like that the applicator is sustainable - I like that the tampons are sanitised to reduce the risk of infection - I like that they are delivered to my door - I like that they are made of 100% organic cotton fibres - I like that the packaging is sustainable - I like the water-soluble wrapper - None of the above - Other	
3.	Approximately how many Nude tampons do you use each month?	- None - Less than 5 - Between 5 and 10 - More than 10 - More than 20	
4.	Approximately how many CBD tampons do you use each month?	- None - Less than 5 - Between 5 and 10 - More than 10 - More than 20	If None is entered, jump to Q19

5.	Do you agree with any of the following statements about Daye's CBD tampons?	- They have removed my menstrual pain entirely - They have reduced my menstrual pain - I use fewer pain-killers with the CBD tampon - I have fewer infections like thrush, yeast, UTIs or bacterial vaginosis (BV) after using the CBD tampon - I have noticed other physical benefits - None of the above - Other	If the answer includes 'I have noticed other physical benefits' jump to Q6. In all other cases, jump to Q7.
6.	Can you tell us more about any additional physical benefits you may have experienced?	Open text	
7.	What do you dislike about the CBD tampons?	- I didn't experience pain-relief - I don't find the tampons comfortable - The tampons leaked menstrual blood - I need a smaller size tampon - I need a higher absorbency tampon - The packaging could be more sustainable - I've experienced negative side-effects from the tampons - The applicator doesn't work well for me - The applicator isn't sustainable - The tampons are a hassle to store - The price was too high - The delivery took too long - The box didn't fit through my letterbox - Nothing - Other	

8.	Please, rate the severity of your menstrual cramps before using the CBD tampons	Use the following scale 0 — No pain 1 — Very minor annoyance with occasional minor twinges. No medication is needed. 2 — Minor annoyance with occasional strong twinges. No medication is needed. 3 — Annoying enough to be distracting. Mild painkillers like Aspirin, Ibuprofen or Tylenol are effective. 4 — Can be ignored if you are really involved in your work, but still distracting. Mild painkillers relieve the pain for 3-4 hours. 5 — Can't be ignored for more than 30 minutes. Mild painkillers relieve the pain for 3-4 hours. 6 — Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers like Codeine and Vicodin reduce the pain for 3-4 hours. 7 — Makes it difficult to concentrate, and interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective. The strongest painkillers (like Oxycontin and Morphine) relieve the pain. 8 — Physical activity is severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain. Stronger painkillers are minimally effective. Strongest painkillers reduce pain for 3-4 hours. 9 — Unable to speak. Crying out or moaning uncontrollably near delirium. Strongest painkillers are only partially effective. 10 — Unconscious. Pain makes you pass out. Strongest painkillers are only partially effective.	

9.	Please, rate the severity of your menstrual cramps whilst using the CBD tampons	Use the following scale 0 — No pain 1 — Very minor annoyance with occasional minor twinges. No medication is needed. 2 — Minor annoyance with occasional strong twinges. No medication is needed. 3 — Annoying enough to be distracting. Mild painkillers like Aspirin, Ibuprofen or Tylenol are effective. 4 — Can be ignored if you are really involved in your work, but still distracting. Mild painkillers relieve the pain for 3-4 hours. 5 — Can't be ignored for more than 30 minutes. Mild painkillers relieve the pain for 3-4 hours. 6 — Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers like Codeine and Vicodin reduce the pain for 3-4 hours. 7 — Makes it difficult to concentrate, and interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective. The strongest painkillers (like Oxycontin and Morphine) relieve the pain. 8 — Physical activity is severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain. Stronger painkillers are minimally effective. Strongest painkillers reduce pain for 3-4 hours. 9 — Unable to speak. Crying out or moaning uncontrollably near delirium. Strongest painkillers are only partially effective. 10 — Unconscious. Pain makes you pass out. Strongest painkillers are only partially effective.	

10.	Have you been diagnosed by a GP/OBGYN with any gynaecological conditions?	- Yes - No	If 'No', skip to Q12
11.	What is your current diagnosis?	- Adenomyosis - Endometriosis - Primary Dysmenorrhea - Pelvic inflammatory disease (PID) - Polycystic ovarian syndrome (PCOS) - Other	
12.	Do you find yourself needing fewer painkillers when using the CBD tampons?	- Yes, everytime - Most of the time - Sometimes - No, never - Not sure - Other	
13.	When do you use the CBD tampons?	- Only when I start feeling cramps - First day of my period - First two days of my period - First three days of my period - During my entire cycle - Never - Other	
14.	Have you ever experienced any of the following positive symptoms when using the CBD tampons?	- Pain relief - Reduced stress/anxiety - Better sleep - Better mood - Better perceived quality of life - Better digestion, less bloating - Reduced back pain - Reduced headaches - Reduced vaginal infections (Eg. Thrush, abnormal discharge) - Reduced rate of UTI infections - Increased energy levels - Other	If the answer includes 'pain relief', jump to Q15-Q16. In all other cases jump to Q17.
15.	On average, how long after insertion, does it take for you to feel the pain relieving effects of Daye's CBD tampons?	- Almost immediately - Within 15 minutes - Within 30 minutes - Within 45 minutes - 1 hour or more - Other	

16.	On average, how long after insertion, does pain relief from Daye's CBD tampons last?	- Less than 30 minutes - 1 - 2 hours - 2 - 4 hours - 4 - 6 hours - 7 + hours - Other	
17.	Have you ever experienced any of the following side-effects when using the CBD tampons?	- Worsening cramps - Irritation - Allergic reaction - Thrush - Skin injury from the applicator - Vaginal itching - Vaginal discomfort - Vaginal swelling - Dizziness - Fever - Nausea - Abnormal discharge - None of the above - Other	
18.	Have you ever experienced these symptoms when using other brands of tampon?	- Yes - No - Not sure	
19.	Approximately how many Regular tampons do you use each month?	- None - Less than 5 - Between 5 and 10 - More than 10 - More than 20	
20.	Approximately how many Super tampons do you use each month?	- None - Less than 5 - Between 5 and 10 - More than 10 - More than 20	
21.	Please, can you rate how absorbent you find the tampon?	0 = very unabsorbent 5 = extremely absorbent	
22.	Please, can you rate how comfortable you find the tampon during wear?	0 = very uncomfortable 5 = extremely comfortable	
23.	Please, can you rate how easy you find the applicator to use?	0 = very difficult to use 5 = extremely easy to use	

24.	How likely are you to refer Daye to a friend?	0 = very unlikely 10 = extremely likely	
25.	We’d love to hear your thoughts on our tampons! Please share how using them has impacted your menstrual health and comfort	Open text	
26.	Would you be willing to let us anonymously share your feedback to help others learn about Daye's tampons?	- Yes, you can share my feedback anonymously - No, I prefer my feedback to remain private	

Supplementary material 2

Table 12: Mankoski pain scores for severity of menstrual cramps before and during CBD tampon use amongst active (n=1210) and non-active CBD tampon users (n=913) who responded to the survey

	Active users (n=1210), n (%)	Non-active users (n=913), n (%)
Severity of menstrual cramps before CBD tampon use		
0	3 (0.2)	3 (0.3)
1	12 (1.0)	8 (0.9)
2	31 (2.6)	35 (3.8)
3	53 (4.4)	56 (6.1)
4	103 (8.5)	85 (9.3)
5	167 (13.8)	118 (12.9)
6	179 (14.8)	147 (16.1)
7	279 (23.1)	160 (17.5)
8	235 (19.4)	179 (19.6)
9	83 (6.9)	46 (5.0)
10	55 (4.5)	58 (6.4)
Missing	10 (0.8)	18 (2.0)
Severity of menstrual cramps during CBD tampon use		
0	38 (3.1)	40 (4.4)
1	126 (10.4)	98 (10.7)
2	231 (19.1)	170 (18.6)
3	201 (16.6)	150 (16.4)
4	184 (15.2)	131 (14.3)
5	139 (11.5)	101 (11.1)
6	144 (11.9)	101 (11.1)
7	89 (7.4)	70 (7.7)
8	36 (3.0)	28 (3.1)

9	9 (0.7)	15 (1.6)
10	8 (0.7)	4 (0.4)
Missing	5 (0.4)	5 (0.5)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SafetyandEfficacyofCannabidiolInfusedTamponsforPrimaryDysmenorrhea.Suppmaterial.22.12.2025.docx