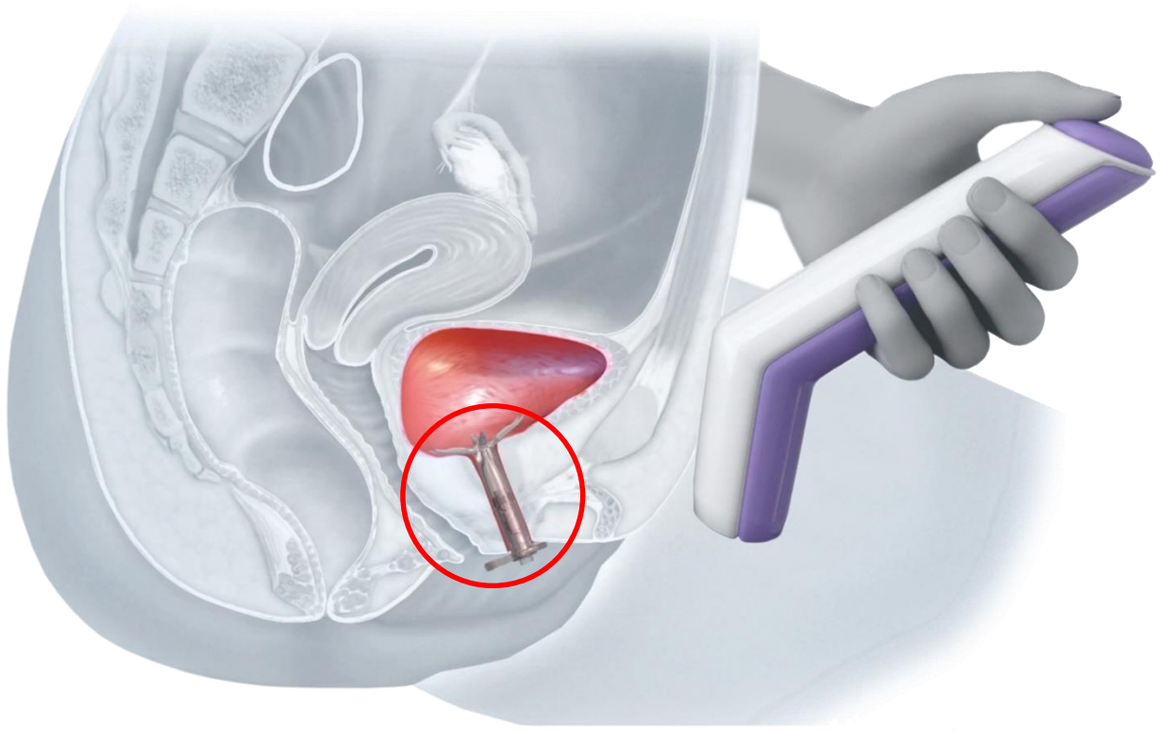
Evidence Summary:

The inFlow™ Urinary Prosthesis

FDA De Novo Approval DEN130044

- Unique alternative to urinary catheters for women with permanent urinary retention
- Therapeutic benefits
  - Highly effective in emptying the bladder
  - Lower UTI rate than CIC (clean intermittent catheterization), the current standard of care
  - Significantly improves quality of life



FDA History as a Class III Device

- The FDA classified inFlow as a Class III device and required that a pivotal trial be conducted under IDE in support of a PMA (premarket approval) application
  - Class III is typically limited to surgical implants and other devices with high-risk
- Vesiflo submitted data from a prospective, multi-center* pivotal trial (*n*=273) that compared inFlow to current standard of care, clean intermittent catheterization (CIC)
  - Additional evidence included:
    - Six non-comparative clinical studies (total *n*=228), three of which were long-term studies of 1-4 years and all of which were published in major peer-reviewed journals
    - Real-world experience as documented by ISO-audited complaint files for 1,250 women-years of clinical use OUS with no MDRs or significant safety issues
    - Animal and laboratory test reports showing conformance to the most recent ISO 10993 biocompatibility standards for a permanent surface device with mucosal membrane contact
    - Laboratory test reports showing conformance to ISO, ASTM and other established industry standards for urinary catheters
    - A microbiology study showing >8.4x better encrustation resistance than current standard of care
- Following its review of all evidence and particularly the favorable safety data from the pivotal trial, the FDA down-classified the inFlow from Class III to Class II
  - The inFlow was approved via the De Novo pathway, establishing a new device type

* 15 US sites, 3 sites OUS

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Pivotal Trial Design, a LoE Ib Study

- The pivotal study compared the inFlow to the current standard of care (CIC) and did so with a cohort for which CIC was their normal method of bladder drainage
  - Study limited to women with a urodynamically confirmed Dx of IDC who were successfully using CIC, some for as long as 20 years
  - Single-arm crossover design in which each subject acted as her own control
  - CIC use tracked for 8 weeks as Baseline, then switched to inFlow Treatment for 16 weeks
- Relevant clinical endpoints were selected

1. **Primary Endpoint: Post-void residuals (PVRs)** - Indicates how effectively each device performs its primary function, draining the bladder
   - PVRs were considered comparable for a subject if their median inFlow/Treatment PVR was no greater than their median CIC/Baseline PVR, or if both were <50 cc
   - Goal was to have at least 95% of subjects with comparable rate PVRs
2. **Secondary Endpoint: Quality of life per Wagner I-QOL** – As measured on a 100-point scale using a validated instrument that is commonly used for voiding-related studies
   - Goal was to show equivalence
3. **Comparative Safety:** Adverse events, particularly the two most serious catheter-related complications, urinary tract infection (UTI) and encrustation

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Enrollment Criteria and Subject Flowchart

- Key inclusion criteria
  - Women 18 years of age or older
  - Mentally coherent and either have sufficient manual dexterity to operate (and if necessary remove) device or be assisted by a caregiver
  - Urodynamically confirmed diagnosis of “atonic bladder” (now IDC)
  - Capable of determining when to void (either by urge or by adherence to timed voiding schedule) or has caregiver who will attend to bladder emptying at least 4x daily

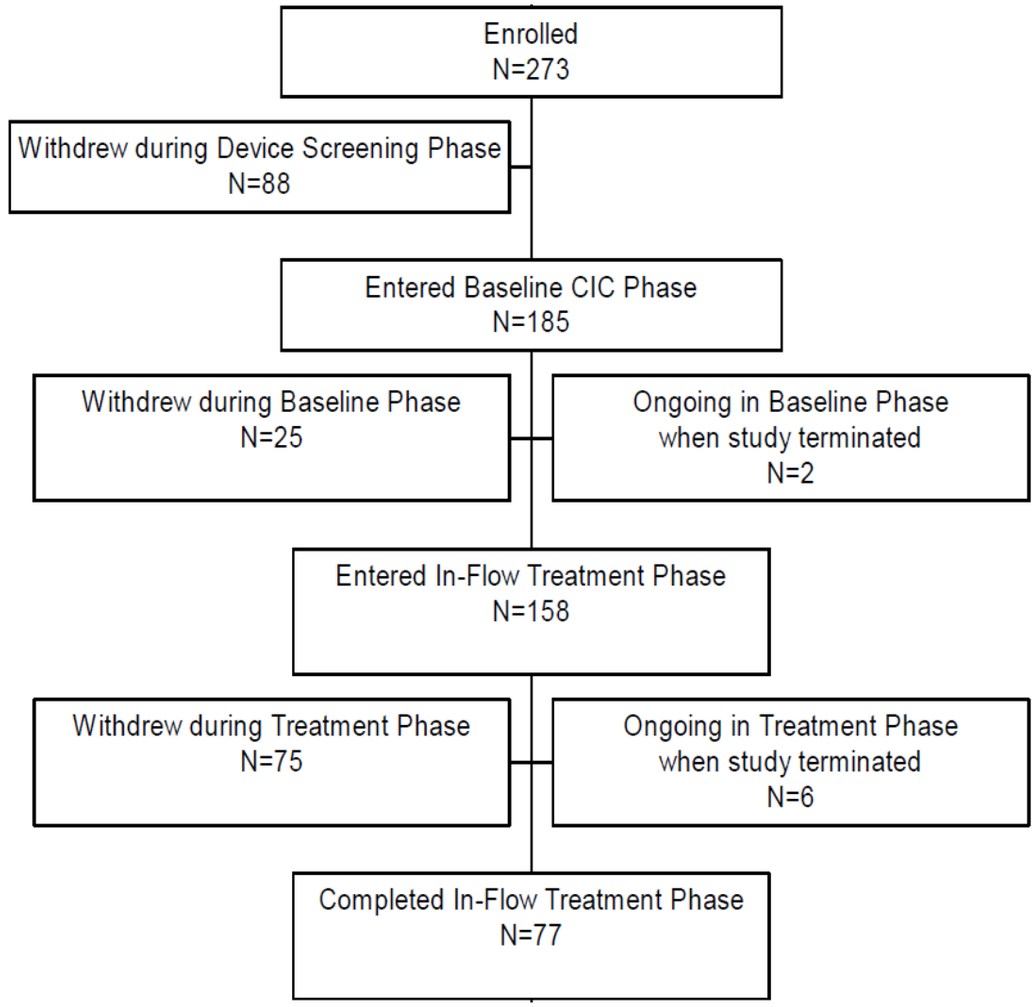
- Key exclusion criteria
  - Diagnosis and/or treatment of a symptomatic UTI during the two weeks prior to the screening visit
  - Uninhibited bladder contraction >15cm H_20 unless confirmed via UDS as controlled with anticholinergics
  - Neoplastic or inflammatory processes involving the lower urinary tract, uterus, cervix, or vagina
  - Psychiatric or physical condition which would impede the ability of a subject to follow instructions for use of the external control unit or to remove the device if necessary, unless a trained caregiver will attend to bladder emptying for the subject at least four times daily

Baseline/CIC = 8 weeks

Then Crossed Over to

Treatment/inFlow = 16 weeks

Pt1 = T1-T7 (Weeks 1-8) and Pt2 = T8-T16 (Weeks 9-16)



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Primary Endpoint: Post-Void Residual (PVR)

The inFlow and CIC were equivalent in their ability to fully empty the bladder

- 98% (113/115) of evaluable subjects had comparable PVRs, with median PVR at each visit during inFlow Treatment ranging from 10-20cc
  - 1-sided exact 95% confidence lower limit: 95%; 2-sided exact 95% confidence interval 94-99.8%
    - These results successfully met the protocol stated goal of demonstrating a 95% comparable rate with a 95% confidence interval half-width of approximately ±4%
  - 92-98% of all subjects had comparable PVRs at every treatment visit (p<0.0001)
- Subjects were considered evaluable if they had both Baseline and Treatment PVR data
  - There was no statistically significant difference in Baseline PVR between those included vs. excluded in PVR analysis (P=0.54 by stratified logrank test)
- The within patient inFlow vs. CIC difference indicated a statistically significant lower PVR on inFlow (p=0.02)
  - Both inFlow and CIC were highly effective, with median values well below the 50-75cc level considered acceptable voiding function

PVR Volumes	N	Median
Baseline (CIC)	115	13cc
Treatment (inFlow)	115	10cc

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Secondary Endpoint: Quality of Life (QOL)

The inFlow was significantly superior to CIC in its effect on quality of life

- Incontinence-related QOL was measured by the Wagner I-QOL on a 100-point scale (higher scores are better)
  - In order to better isolate device-specific affects, responses were analyzed in two parts

Wagner I-QOL Part A - Satisfaction with Current Type of Catheter	N	Mean	Std. Dev	Median	Minimum	Maximum	P-value*
Baseline Mean QOL	85	48.9	24.4	53.5	0.0	97.0	
Treatment Mean QOL	85	86.4	15.0	92.0	39.4	100.0	
Treatment − Baseline Difference	85	37.5	28.8	36.1	-24.2	100.0	<0.0001
Percent Change over Baseline**	84	225%	536%	69%	-29%	3300%	<0.0001

Wagner I-QOL Part B - Modified Wagner Questionnaire	N	Mean	Std. Dev	Median	Minimum	Maximum	P-value*
Baseline Mean QOL	85	42.2	25.8	40.2	0.0	100.0	
Treatment Mean QOL	85	67.4	24.5	68.0	7.1	100.0	
Treatment − Baseline Difference	85	25.2	26.1	21.5	-22.3	90.8	<0.0001
Percent Change over Baseline**	84	157%	267%	54%	-45%	1383%	<0.0001

*Paired t test **Percent change not calculated if Baseline=0

  - Subjects were considered evaluable if they had both Baseline and Treatment QOL data
    - Based on within-subject QOL scores during Baseline (S1, B3, T1) and Treatment phases (T4, T7, T11, T16)
    - There was no statistically significant difference in mean Baseline score between those included vs. excluded in QOL analysis (42.2 vs. 45.8: p=0.30 by linear regression)

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Comparative Safety: All Adverse Events

There were no unanticipated adverse events, no serious or long-lasting AEs

- As is common with urinary catheters, adverse events were frequent but minor
  - Rates generally decreased from the first half to the second half of Treatment phase, with the exception of bladder inflammation and all of those events were mild in severity

All Reported Events - Completers Only (n=77)	Baseline (Pt Months=179)		Treatment T1-T7 (Pt-Months=133)		Treatment T7-T16 (Pt-Months=189)		Treatment T1-T16 (Pt-Months=322)	
Adverse Event	**Events**	**Rate**	**Events**	**Rate**	**Events**	**Rate**	**Events**	**Rate**
Asymptomatic Bacteriuria	31	0.17	18	0.13	24	0.13	42	0.13
Bladder Inflammation	0	0	0	0	8	0.04	8	0.02
Frequency, Urgency, Bladder Spasms	10	0.06	13	0.10	7	0.04	20	0.06
Gastrointestinal Disorder	10	0.06	3	0.02	10	0.05	13	0.04
Genitourinary Pain	10	0.06	15	0.11	16	0.08	31	0.10
Hematuria / Scant Perineal Bleeding	1	0.01	3	0.02	4	0.02	7	0.02
Urinary Incontinence	14	0.08	40	0.30	37	0.20	77	0.24
Urinary Tract Infection	21	0.12	15	0.11	16	0.08	31	0.10
Vulvovaginal / Periurethral Disorders	11	0.06	12	0.09	10	0.05	22	0.07
Total, All Adverse Events	140	0.78	182	1.36	213	1.13	395	1.23

- Includes all occurrences of any adverse event during the specified period
- No statistically significant differences between Baseline and Treatment except genitourinary pain during T1-T7, bladder inflammation post T7 through T16, and urinary incontinence and all adverse events combined throughout Treatment
- Although based on Completers in order to compare study phases for the same set of subjects, safety profiles of subjects who dropped out did not differ in any clinically significant way from those who completed the study and thus provide no evidence of survivor bias

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Comparative Safety: UTI Rate

The inFlow's UTI rate was the same or lower than that for CIC

- *Indwelling* catheters are known to have an exceedingly high UTI rate compared to *intermittent* catheters, primarily due to the difference in device exposure times
  - As the inFlow is an indwelling device, its UTI rate was a prospective concern

Study Phase	Number Subjects	Total Patient Months	UTI Events	UTI Rate
Pivotal-Baseline (CIC)	77	179	21	0.12
Pivotal-Treatment T1-T7 (inFlow)	77	133	15	0.11
Pivotal-Treatment T7-T16 (inFlow)	77	189	16	0.08

- Based on Completers only in order to compare study phases with the same set of subjects
- Total UTI experience in pivotal trial = 157 subjects and 417 patient-months device exposure

- The inFlow's UTI rate started slightly lower than that for CIC and declined with continued use

Safety: Encrustation

No encrustation was reported

- Encrustation occurs in ~50% of patients with indwelling urinary catheters and along with UTI, is the most significant clinical problem associated with their use
  - Although a non-comparative measure, since inFlow is an indwelling device, encrustation rate was a prospective concern and so was tracked in the pivotal using a 4-point scale

- Following the pivotal, an *in vitro* study *by* Stickler showed inFlow's encrustation resistance to be **>8.4x superior** to an all-silicone Foley, the current gold standard:

"Under conditions that simulated a heavy infection of P. mirabilis, where a conventional Foley catheter blocked with crystalline biofilm after 25.7 hours, the inFlow device drained the bladder for at least 9 days… (its) central lumen appeared to be essentially clear."

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Summary of Pivotal Trial Results

All clinical endpoints were met or exceeded

Primary Endpoints

Effectiveness
- PVR
- QOL

- Primary Endpoint - Post-Void Residual (PVR)
  - The inFlow and CIC were equivalent in their ability to fully empty the bladder
- Secondary Endpoint - Quality of Life (QOL)
  - The inFlow was significantly superior to CIC in its effect on quality of life

Safety
- All Adverse Events
- UTI Rate
- Encrustation

- All Adverse Events
  - No unanticipated adverse events, no serious or long-lasting AEs
- UTI Rate
  - The inFlow's UTI rate was the same or lower than that for CIC
- Encrustation
  - No encrustation was reported

Actual exposure time far exceeded prospective goals (2928 weeks vs. 1220 weeks) and device met its primary endpoint for almost 100% of subjects

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Discussion of Device Acceptance

- Device acceptance was an anticipated issue in the pivotal trial
  - As prospectively estimated, 50% of subjects discontinued use for device-related reasons, most in first 1-4 days due to discomfort or leakage
- On-device trial was shown to be an effective predictor of success
  - No harm was done to failed patients – they simply resumed CIC
- Chronic voiding disorders are known to be medically problematic and acceptance of most device-based interventions has historically been limited
  - Per FDA SSED reports* acceptance rates in the pivotal trials for other currently covered devices for chronic voiding disorders were similar to that for the inFlow
    - The device acceptance rate for the Rochester Medical FemSoft® intraurethral insert for stress urinary incontinence (SUI) was 22.7% of 300 subjects screened or 45.33% of 150 subjects who entered the 12-month study (and UTI rate was high)
    - Of 157 subjects who were implanted with the Medtronic InterStim® for overactive bladder only 43 (9.4% of 458 those screened or 27.39% of 157) completed the 12-month study
- Following the pivotal, Lynch showed inFlow device acceptance can be increased by providing pre-insertion patient education and post-insertion nursing support

* Summary of Safety and Effectiveness Data

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Safety Profile

- The inFlow's pivotal trial showed it to have a favorable safety profile
  - No serious or lasting adverse events associated with inFlow use were reported
  - inFlow's UTI rate was the same or better than that for *intermittent* catheters, an unprecedented finding for an *indwelling* device
  - There were no adverse tissue changes, as confirmed by cystoscopic examination - the device does not alter the anatomy
  - No device failed due to encrustation
  - Importantly, inFlow can be easily and safely removed at any time, even by patients
    - Discomfort or leakage that resulted in dropout was promptly resolved with device removal
- The FDA's review of the safety data from the pivotal trial was the primary determinant in its decision to down-classify the inFlow from Class III to Class II

Summary

- The inFlow is of significant benefit to those who can use it
  - Demonstrated effectiveness in emptying the bladder
  - Significantly improved quality of life compared to CIC
  - Favorable safety profile and a lower UTI rate than CIC
  - 97.4% (75/77) of subjects who completed the Treatment phase of the inFlow's pivotal trial opted-in to continue using inFlow afterward
- Most device candidates can be easily and safely identified with an on-device trial

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Supporting Clinical Studies

- Six non-comparative clinical studies (total *n*=228) with similar populations to the pivotal have been published in major peer-reviewed journals
  - Results were similar - no serious or lasting adverse events were reported, reported UTI rates were consistently low and best practice became better understood over time

PI/Lead Author	Journal	Study Size	UTI Rate*	Key Findings/ Conclusions
Lynch	British Journal of Urology	20	0.01	Lynch reported that 14 evaluable subjects had a total of 2 UTIs in 156 subject-months (0.01% incidence), almost no device-related dropout, 80% quality of life improvement per Wagner I-QOL scores, no negative tissue changes and concluded that "*the (inFlow) device provides an effective method of bladder drainage, with few side-effects and significant improvement in QoL.*"
Mazouni	European Journal of Obstetrics and Gynecology	60	0.03	Mazouni reported that although 30 subjects dropped out <15 days, 30 evaluable subjects had a total of 6 UTIs in 178 subject-months (3.4% incidence) and concluded that inFlow is *"An attractive, simple technique for use as an alternative to catheterization."*
Madjar	European Urology	21	0.01	Madjar reported that when 21 subjects from his two-part study continued on-device, they had a total of 4 UTIs in 517 subject-months (0.01% incidence) and concluded that, although dropout was a problem (due largely to discomfort), *"all patients were satisfied with the device and preferred it to previous treatment modalities used."*
Madjar	American Urological Association	92	0.04	Madjar reported that in the first phase of his two-part study, 47 subjects had a total of 14 UTIs in 357 subject-months (3.9% incidence) and all resolved with oral antibiotics.
Schurch	British Journal of Urology	18	Not Reported	Early study suffered from poor transition of a new technology to clinical practice and product quality issues.
Nativ	American Society for Artificial Internal Organs	17	0.03	Nativ reported that 14 evaluable subjects had a total of 3 UTIs in 118 subject-months (0.025% incidence). Interestingly, 2 subjects recovered bladder function after prolonged inFlow use (as did 8 subjects in other studies, total 10/228=4.4%).
Totals/Average		228	0.02**	207 unique subjects (Madjar studies were continuous for same cohort)

* UTI rate was not a prospective measure in the studies cited. This table is based on a retrospective analysis of studies reporting UTI rates.

** The five studies reporting UTI rates reported a total of 29 UTIs in 1,326 subject-months.

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Animal and Laboratory Testing

Test Type	Tests Conducted
Biocompatibility	As the inFlow is classified as a permanent surface device with mucosal membrane contact and per ISO 10993-1:2009 (Biological Evaluation of Medical Devices), the following biocompatibility tests were performed on final, sterilized samples: • ISO 10993-5 Cytoxicity • ISO 10993-10 Sensitization • ISO 10993-10 Irritation • ISO 10993-3 Genotoxicity • ISO 10993-6 Implantation (for both 13 weeks and 26 weeks) In addition, the following additional tests were performed re the systemic toxicity of device materials: • Chemical analysis of nonvolatile leachables from the silicone elastomer • Biocompatibility testing on the internal magnet assembly: Cytotoxicity, Intracutaneous reactivity and Acute systemic toxicity • Corrosion testing of the internal magnet assembly Per the FDA "The results of this testing support the biocompatibility of the inFlow device for its intended use." In 2016, new animal-based biocompatibility tests were conducted in Korea to confirm conformance to the most current ISO standards: • ISO 10993-10:2013 Skin Sensitization Testing • Subacute Toxicity Testing (4-week implantation)
Sterilization	Complies with ISO 11137-2, Sterilization of Health Care Products - Radiation
Additional Applicable Standards*	Laboratory tests demonstrated that the inFlow device and Activator meet their performance specifications and, where applicable, conform to ISO, ASTM and other recognized standards: • Catheter Pull-out Force Testing (as per "Inflated Balloon Response to Traction" test in ASTM F623-89 Standard Performance Specification for Foley Catheters) • Catheter Flow Rate Testing (as per "Flow Rate through Drainage Lumen" test in ASTM F623-89) • Catheter's DC Magnetic Field Levels (Alpen Committee standards) • Activator DC Magnetic Field Testing (Alpen Committee standards) • Activator AC Magnetic Field Testing (IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields 3 kHz to 300 GHz)
Device-Specific Tests*	A number of bench studies, including the following, demonstrated that the inFlow device and Activator meet design-related performance specifications: • High Pressure Test (seal maintained under 200 cm H20 bladder pressure) • Catheter Pump and Valve Endurance Test (1140 voiding cycles=6 months use) • Activator Endurance Testing (11,552 operation cycles=5 years) • Activator Drop Testing (50 cm onto hard surface) • Activator Battery Endurance Testing (2 months)

* Not a complete list of tests conducted