### Long Term Infusion Using ALZET® Osmotic Pumps

ALZET pumps range in duration from 24 hours to 6 weeks. Animals can be dosed for periods which exceed the duration of a single pump by serial reimplantation of fresh pumps. This collection of references includes only the most recent citations. However, we do have older references which include infusions of as long as 3 years and in which up to 52 serial implantations have been performed on a single animal. The following table indicates the longest published duration of administration by animal along with a reference. *(In some cases, more than one study infused for this duration.)*

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DURATION</th>
<th>PUMPS REPLACED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Rabbit</td>
<td>36 weeks</td>
<td>Every 4 weeks</td>
<td>P8478 Ma T Modulation of allograft incorporation by growth factors over a prolonged continuous infusion of duration in vivo. Bone 2007; 41(3):386-392</td>
</tr>
</tbody>
</table>

The short abstract following each reference in the attached list details the substance(s) infused, route of administration, animal model studied, solvent(s), model of pump, duration of infusion, and whether stress to the animal was noted.

**Note:** This list does not contain references in this category from before the years specified. To obtain a complete listing of earlier references, contact ALZET Technical Services at 800-692-2990 (U.S. & Canada) or by email at alzet@durect.com.
Recent References (2017-2020) on the Long Term Administration of Agents Using ALZET® Osmotic Pumps


**Agents:** Dihydrotestosterone  **Vehicle:** Not stated;  **Route:** SC;  **Species:** Rat;  **Pump:** Not stated;  **Duration:** 90 days;

**ALZET Comments:** Dose (83 μg/day); Controls received mp w/ vehicle; animal info (female Wistar albino rats, 21 days old); long-term study; Dihydrotestosterone aka DHT; dependence;


**Agents:** Metoprolol  **Vehicle:** Not stated;  **Route:** SC;  **Species:** Mice;  **Pump:** 1004;  **Duration:** 3 months; 2 months;

**ALZET Comments:** Dose (5 mg/kg/day); Controls received mp w/ vehicle; animal info (male mice, 3.5 months old; female mice, 6 months old); behavioral testing (Morris Water Maze; Fear Conditioning); pumps replaced every 4 weeks; long-term study; neurodegenerative (Alzheimer’s);


**Agents:** Vasoactive intestinal peptide  **Vehicle:** Hartmann’s Solution;  **Route:** IV (iliac);  **Species:** Rat;  **Pump:** Not stated;  **Duration:** 14 weeks;

**ALZET Comments:** Dose (5 pmol/kg/min); Controls received mp w/ vehicle; animal info (Fourteen week old spontaneous hypertensive rat); long-term study; Blood pressure measured via tail cuff plethysmography;193 mmHg - 200 mmHg;Vasoactive intestinal peptide aka VIP; peptides; dependence;


**Agents:** Relaxin  **Vehicle:** Saline;  **Route:** IP;  **Species:** Rat;  **Pump:** Not stated;  **Duration:** 12 weeks;

**ALZET Comments:** Dose (0.17 μg/hr); Controls received mp w/ vehicle; animal info (Sprague Dawley rats); pumps replaced every 4 weeks; long-term study; dependence;


**Agents:** Cyclosporine A  **Vehicle:** Ethanol, Cremophor;  **Route:** SC;  **Species:** Rat;  **Pump:** 2ML4;  **Duration:** 56 days;

**ALZET Comments:** Dose (15 mg/kg/day); animal info (male Sprague-Dawley rats, 350 g); post op. care (3 mg/kg ketoprofen); behavioral testing (Montoya staircase and tapered beam test); long-term study; ischemia (stroke);


**Agents:** ASB20123  **Vehicle:** Not Stated;  **Route:** SC;  **Species:** Rat;  **Pump:** Not Notated;  **Duration:** 1 week, 12 weeks;

**ALZET Comments:** Dose (0.05, 0.15 mg/kg/day); dose-response (fig 5); Controls received mp w/ vehicle; animal info (Seven-week-old male SD rats); comparison of injections vs mp “We also analyzed whether continuous sc infusion of ASB20123 to rats could accelerate skeletal growth, compared to the effects of multiple sc bolus injections”; long-term study; ASB20123 is a CNP/ghrelin chimeric peptide, composed of CNP(1-22) and human ghrelin (12-28, E17D); peptides; replacement therapy (dwarf);


**Agents:** Pyridostigmine Bromide; Donepezil  **Vehicle:** Not Stated;  **Route:** SC;  **Species:** Rat;  **Pump:** 2004;  **Duration:** 16 weeks;

**ALZET Comments:** Dose (Pyridostigmine bromide at 1.5 mg/kg/day; Donepzeil at 1.4 mg/kg/day); animal info (5 week old male SHR and Wistar Kyoto rats); pumps replaced every 4 weeks; long-term study; enzyme inhibitor (Pyridostigmine Bromide inhibits plasma acetylcholinesterase activity; Donepezil inhibits brain acetylcholinesterase activity); cardiovascular; Four pump replacements were performed; BP measured via Tail-cuff method;
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Bibliography

Q7616: A. Kurdi, et al. Everolimus depletes plaque macrophages, abolishes intraplaque neovascularization and improves survival in mice with advanced atherosclerosis. Vascul Pharmacol 2019;113(70-76

Agents: everolimus Vehicle: DMSO; propylene glycol; ethanol, buffered; Route: SC; Species: Mice; Pump: 1004; Duration: 12 weeks;

ALZET Comments: "Dose (1.5 mg/kg/day); 50% DMSO, 40% propylene glycol, 10% absolute ethanol supplemented with 0.4 μl/ml Tween 20 used; animal info (6 weeks, female, ApoE(-/-)FbnI(C1039G+/-)); pumps replaced every 4 weeks; long-term study; cardiovascular; "'"Four out of 12 control animals died abruptly during the experiment, which is a phenomenon that started at 21 weeks of WD (corresponding with 9 weeks of treatment with vehicle solution).''' p.72; Therapeutic indication (stabilizes atherosclerotic plaques and reduce atherosclerosis-driven complications such as cardiac hypertrophy and fibrosis, brain hypoxia and sudden death); "


Agents: Murine Oncostatin M Vehicle: PBS; Route: SC; Species: Mice; Pump: 1004; Duration: 16 weeks;

ALZET Comments: Dose (10 or 30 μg/kg/day); Controls received mp w/ vehicle; animal info (female APOE3Leiden.CETP transgenic mice (10–15 weeks of age)); pumps replaced every 5.5 weeks; long-term study; Murine Oncostatin M aka Murine OSM; cardiovascular;


Agents: Quinic acid Vehicle: Saline; Route: SC; Species: Mice; Pump: Not stated; Duration: 12 weeks;

ALZET Comments: Dose (75 mg/kg/day); Controls received mp w/ vehicle; animal info (12 weeks old, Male, C57BL/6N); pumps replaced every 7 weeks; Multiple pumps per animal (); long-term study; Quinic acid aka QA ; dependence;

Q7525: C. Hartmann, et al. Angiotensin II-induced hypertension increases the mutant frequency in rat kidney. Archives of Toxicology 2019;93(7):2045-2055

Agents: Angiotensin II Vehicle: Saline; Route: SC; Species: Rat; Pump: 2004, 2006; Duration: 20 weeks;

ALZET Comments: Dose (400 μg/kg/day); Controls received mp w/ PBS; animal info (5-8 weeks old, Male); pumps replaced every 7 weeks; long-term study; cardiovascular;

Q8009: D. Gittings, et al. Chronic Nicotine Exposure Alters Uninjured Tendon Vascularity and Viscoelasticity. Foot & Ankle Orthopaedics 2019;4(2): 0.9% Saline used; Controls received mp w/ vehicle; animal info (Sprague Dawley, 10-13 weeks old, 367-425 g); long-term study; dependence;

Q7276: P. Y. Chu, et al. CXCR4 Antagonism Reduces Cardiac Fibrosis and Improves Cardiac Performance in Dilated Cardiomyopathy. Front Pharmacol 2019;10(117

Agents: AMD3100 Vehicle: Water; Route: Not Stated; Species: Mice; Pump: 2004; Duration: 12 weeks;

ALZET Comments: Dose (6 mg/kg per day,); animal info (male mice age 6 weeks); long-term study; CXCR4 antagonist aka AMD3100; cardiovascular;


Agents: Exendin-4 Vehicle: Not stated; Route: SC; Species: Mice; Pump: Not stated; Duration: 2 weeks;

ALZET Comments: Dose (24 nmol/kg/day); Controls received sham surgery; animal info (10 weeks, male, C57BL/6J and db/db); ischemia (coronary artery occlusion); cardiovascular; diabetes; "As there has been no published protocol for long-term EX administration in mice, we followed the initial EX injection with prolonged Exendin-4 administration via osmotic pump for 2 weeks" p.35-36;

**Agents:** SOD1-Derlin-1 inhibitor #56-40, SOD1-Derlin-1 inhibitor #56-59  
**Vehicle:** DMSO;  
**Route:** CSF/CNS (lateral ventricle);  
**Species:** Mice;  
**Pump:** 2006;  
**Duration:** 58 weeks;  
**ALZET Comments:** Dose (1 mM #56-40 or 3 mM #56-59); Controls received mp w/ vehicle; animal info (22 weeks, male, C57BL6/6); behavioral testing (rotarod performance); pumps replaced every 6 weeks until mouse showed paralysis onset; long-term study; stability verified by (in-vitro immunoprecipitation assay); 3-Amino-N-(4-pyridyl)-6-(3-pyridyl)thieno[2,3-b]pyridine-2-carboxamide aka #56-40; N-Allyl-3-amino-N-phenyl-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carboxamide aka #56-59; enzyme inhibitor (SOD1-Derlin-1 interaction); ALZET brain infusion kit 3 used; neurodegenerative (Amyotrophic lateral sclerosis);


**Agents:** Nicotine  
**Vehicle:** Saline;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 2004;  
**Duration:** 1 or 6 months;  
**ALZET Comments:** Dose (0.4 mg/kg/h and 2.0 mg/kg/h); dose-response (); dose-response (); pumps replaced every 4 weeks; long-term study; stress/adverse reaction: Mice treated with the higher nicotine dose (2.0 mg/kg/h) lost weight after surgery and 50% died after one week. This was as a result of combined toxic effects of isoflurane and a higher dose of nicotine. Therefore, pentobarbital was used instead of isoflurane for induction of anesthesia, which reduced the mortality rate and improved weight gain in the higher dose group. (see pg. 172);


**Agents:** αKlotho protein, recomb.  
**Vehicle:** Saline;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 1004;  
**Duration:** 20 weeks;  
**ALZET Comments:** Dose (0.3 mg/kg/month); Controls received mp w/ vehicle; long-term study; Therapeutic indication (Acute kidney injury);


**Agents:** Ac-SDKP  
**Vehicle:** Not Stated;  
**Route:** SC;  
**Species:** Rat;  
**Pump:** Not Stated;  
**Duration:** 18 weeks;  
**ALZET Comments:** Dose (3.2 mg/kg/day); animal info (10–12 week old Sprague Dawley rats); long-term study; Ac-SDKP aka N-acetyl-Ser-Asp-Lys-Pro;


**Agents:** Tofacitinib  
**Vehicle:** Saline;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** Not Stated;  
**Duration:** 10 weeks;  
**ALZET Comments:** Dose (100 ug/day); Controls received mp w/ vehicle; tofacitinib is a JAK3 inhibitor; enzyme inhibitor (JAK3);

Q7189: A. U. Joshi, et al. Inhibition of Drp1/Fis1 interaction slows progression of amyotrophic lateral sclerosis. EMBO Molecular Medicine 2018;10(3):

**Agents:** P110-TAT (47-57)  
**Vehicle:** Not Stated;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 28 day pump;  
**Duration:** 60 days;  
**ALZET Comments:** Dose (3 mg/kg/day); animal info (4–6 weeks old AdultB6SJL Tg (SOD1G93A) 1 Gur/J male mice); behavioral testing (Activity chamber); pumps replaced after 30 days; long-term study; P110 is a selective peptide inhibitor of Drp1/Fis1; neurodegenerative (amyotrophic lateral sclerosis); neurodegenerative (amyotrophic lateral sclerosis); stress/adverse reaction: (see pg. 14 );

**Agents:** Uridine, 5-bromo-2′-deoxy  
**Vehicle:** DMSO, Water;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 2002, 2006;  
**Duration:** 9 days and 12 weeks;

**ALZET Comments:** Dose (10 mg/kg/day); 50% DMSO/water used; animal info (16 weeks old male mice); post op. care (bupivacaine, 8 mg/kg, buprenorphine, 0.075 mg/kg); Model 2006 pumps replaced after 6 weeks; long-term study; 5-bromo-2′-deoxyuridine aka BrdU; cardiovascular;


**Agents:** Fingolimod  
**Vehicle:** Saline;  
**Route:** IP;  
**Species:** Mice;  
**Pump:** 1004;  
**Duration:** 8 weeks;

**ALZET Comments:** Dose (1 mg/kg/day); Controls received mp w/ vehicle; animal info (CD86−/− non-obese diabetic (NOD) mice); pumps replaced every 4 weeks; long-term study; Fingolimod is a sphingosine-1-phosphate analogue; neurodegenerative (autoimmune polyneuropathy); stress/adverse reaction: (see pg. 2);


**Agents:** Thyroxine, 3,5,3′-triiodothyronine  
**Vehicle:** NaOH, propylenglycol, PBS;  
**Route:** SC;  
**Species:** Rat (mole rat);  
**Pump:** 2006;  
**Duration:** 12 weeks;

**ALZET Comments:** Dose (90 ng/g of T4, 2 ng/g of T3); 15 mM NaOH, 50% propylenglycol and PBS containing 5% BSA used; Controls received mp w/ vehicle; animal info (Ansell’s mole rats, mean age 2.6 ± 0.92 years); post op. care (Carprofen, 5 mg/kg for at least 3 days; animals were isolated for 24–48 h for recovery then housed as family group); pumps replaced every 6 weeks; long-term study; “Osmotic pumps deliver the test agents with a constant flow rate, thus being well-suited for long-term hormone treatments” pg. 9;


**Agents:** EPZ5676  
**Vehicle:** DMSO, Water;  
**Route:** SC;  
**Species:** Mouse;  
**Pump:** 2006, 2002;  
**Duration:** 8 weeks;

**ALZET Comments:** Dose (1.6 mg/d); 50% DMSO used; Controls received mp w/ vehicle; animal info (Eight-week-old, female, FVB/N); Model 2006 pumps replaced with Model 2002 after six weeks; long-term study; EPZ5676 aka small molecule inhibitor; gene therapy;


**Agents:** Aminobenzotriazole, 1-  
**Vehicle:** Not Stated;  
**Route:** Not Stated;  
**Species:** Mice;  
**Pump:** Not Stated;  
**Duration:** 6, 16 days;

**ALZET Comments:** 1-ABT is a pan-specific, mechanism-based inactivator of the xenobiotic metabolizing forms of cytochrome P450; "Osmotic pumps can be used to maintain maximum blood concentrations of 1-ABT for at least 6 days. Indeed, ALZET osmotic pumps were able to maintain the 1-ABT plasma concentration above 4.1 mg/ml over 336 hours without overt toxicity." p.40. "Furthermore, administration of 1-ABT to mice via an ALZET osmotic pump for 16 days caused no overt toxicity" pg. 41; studies referenced include "Stringer RA, Ferreira S, Rose J, Ronseaux S (2016) Application of osmotic pumps for sustained release of 1-aminobenzotriazole and inhibition of cytochrome P450 enzymes in mice: model comparison with the hepatic P450 reductase null mouse. Drug Metab Dispos 44:1213-1216." and "Watanabe A, Mayumi K, Nishimura K, Osaki H (2016) In vivo use of the CYP inhibitor 1-aminobenzotriazole to increase long-term exposure in mice. Biopharm Drug Disp 37: 373-378."


**Agents:** Melanotan II  
**Vehicle:** CSF, Artificial;  
**Route:** CSF/CNS (lateral ventricle);  
**Species:** Rat;  
**Pump:** Not Stated;  
**Duration:** 28 days;

**ALZET Comments:** Dose (2 µg/day); Controls received mp w/ vehicle; animal info (10 months, male, F344BN, 360-480g); MTII is a synthetic analog of alpha-MSH; Brain coordinates (1.3 mm posterior to bregma, 1.9 mm lateral to midsagittal
suture, depth of 3.5 mm); Cannula placement verified via a stereotaxic device; Original mini-pumps were replaced after recovery from the surgery through a small incision (1 cm); Therapeutic indication (long-term reduction of body mass independent of caloric reduction);


**Agents:** tetrahydropyridine, 1-methyl-4-phenyl-1,2,3,6-
**Vehicle:** Not Stated; **Route:** SC; **Species:** Monkey; **Pump:** Not Stated; **Duration:** 6 months;

**ALZET Comments:** Dose (0.5 mg/d); animal info (Cynomolgus); long-term study;

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (AKA MPTP) is used to induce Parkinsonism; neurodegenerative (); Pumps were used to induce advanced-stage Parkinsonism in macaques by continuous infusion of MPTP. Agents administered during test were administered orally, not through pump infusion.;


**Agents:** Haloperidol, olanzapine **Vehicle:** Cyclodextrin, 2-Hydroxypropyl-B; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 8 weeks;

**ALZET Comments:** Dose (Haloperidol- 2mg/ kg/ day, Olanzapine-10 mg/kg/ day ); Controls received mp w/ vehicle; animal info (10-week old, male, Sprague-Dawley, 240–250 g); pumps replaced every 4 weeks; long-term study; dependence;


**Agents:** Estradiol, 17b- **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2006; **Duration:** Not Stated;

**ALZET Comments:** Controls received mp w/ 20% cyclodextrin; animal info (male, Sprague Dawley, 250-300g, adult); functionality of mp verified by serum levels; behavioral testing (Morris water maze); replacement therapy (estradiol infusion); long-term study; cardiovascular; Dose (0.05 ug/h); “exogenous E2 replacement produced E2 levels of 25-33pg/ml” (pg 2);


**Agents:** Silodosin **Vehicle:** Hartmann’s solution; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 8 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (female, Sprague Dawley, 6 weeks old); long-term study; diabetes; Dose (0.3 or 1 mg/kg/day);


**Agents:** Leptin; SHU-9119 **Vehicle:** PBS; **Route:** SC; CSF/CNS; **Species:** Mice; **Pump:** 2004; **Duration:** 12 weeks, 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (leptin-deficient ob/ob mice); long-term study; pumps replaced every 28 days; SHU-9119 is a MC4R antagonist; Leptin dissolved in PBS and delivered SC for 12 weeks; SHU-9119 dissolved in saline and delivered ICV for 7 days; Pumps model incorrectly listed as Model 2001D. It should be Model 2004 based on description.


**Agents:** Lixisenatide **Vehicle:** Saline; **Route:** SC; **Species:** Rabbits; **Pump:** 2ML4; **Duration:** 12 weeks;

**ALZET Comments:** Dose (30 nmol/kg/day); Controls received mp w/ vehicle; animal info (Watanabe heritable hyperlipidemic); pumps replaced every 4 weeks; long-term study (12 weeks); Lixisenatide is a GLP-1 receptor agonist;


**Agents:** Black Ink **Vehicle:** PBS; **Route:** CSF/CNS (ventricle); **Species:** Mice; **Pump:** 2006; **Duration:** 50 days;
ALZET® Comments: Dose (PBS with 1:100 black ink); animal info (50-day old male C57BL/6J mice); functionality of mp verified by in vitro priming visualization; ALZET brain infusion kit 3 used; cyanoacrylate adhesive; no stress: The implanted pump and the cannula caused minimal discomfort to the animals and it had no effect on the moving ability (see pg.5); good methods; This report describes an improved method for better fixation of cannula during long-term brain infusion experiments using a non-toxic, soft and elastic silicone spacer.

Agents: ASS234 Vehicle: PBS, DMSO; Route: SC; Species: Mice (transgenic); Pump: 2004; Duration: 4 months;
ALZET Comments: Controls received mp w/ vehicle; animal info (10 weeks old, APPswe/PS1ΔE9); long-term study; pumps replaced every 28 days for 4 months; 3.6% DMSO; neurodegenerative (Alzheimer’s disease); behavioral testing (Object recognition task); enzyme inhibitor (AChE/MAO inhibitor); Therapeutic indication (Alzheimer’s disease, AD); Dose (0.62 mg/kg/day);

Agents: Salbutamol Vehicle: Not Stated; Route: Not Stated; Species: Rat; Pump: Not Stated; Duration: 12 weeks; 5 weeks;
ALZET Comments: Dose (0.5 mg/kg/day); Controls received mp w/ vehicle; animal info (Male 8-week-old ZDF rats); long-term study; Salbutamol is a beta2AR agonist; diabetes;

Agents: Leptin Vehicle: Not Stated; Route: SC; Species: Mice; Pump: Not Stated; Duration: 24 weeks;
ALZET Comments: Dose (5 mg/day; 10 mg/day); Controls received mp w/ vehicle; animal info (10-week-old male ObOb and strain-matched control mice); pumps replaced every 12 weeks; Multiple pumps per animal (2); long-term study;

Agents: Glucosylsphingosine Vehicle: DMSO; Propylene glycol; Route: SC; Species: Mice; Pump: 1004; Duration: 12 weeks;
ALZET Comments: Dose (10 mg/kg/day); 50% DMSO:50% propylene glycol used; Controls received mp w/ vehicle; animal info (Male C57BL/6JRj mice); functionality of mp verified by plasma levels; pumps replaced every 4 weeks; long-term study (12 weeks); Resultant plasma level (between 700 and 900 ng/mL); no stress: The pumps were well tolerated and no mortalities were observed (see pg. 11); good methods (p.10); Lyso-Gb1 levels were strongly elevated after four, eight and 12 weeks (levels ranging between 700 and 900 ng/mL). This represented a >500-fold increase compared with vehicle-treated mice

Agents: Antibody, anti-mouse-GM-CSF, Antibody, rat isotype (IgG2a) Vehicle: PBS; Route: SC; Species: Mice; Pump: 1007D; Duration: 8 weeks;
ALZET Comments: Dose (2.5 μg/d); Controls received mp w/ vehicle; pumps replaced every 4 weeks; long-term study;

Agents: Aminopropionitrile, beta Vehicle: Saline; Route: Not Stated; Species: Rat; Pump: Not Stated; Duration: 12 weeks;
ALZET Comments: Dose (100 mg/kg/day); Controls received mp w/ vehicle; animal info (8 week old male Sprague Dawley); post op. care (analgesia by buprenorphine HCl (1 mg/kg); long-term study; enzyme inhibitor (lysyl oxidase);