References on the Administration of Statin Class Drugs Using ALZET® Osmotic Pumps

1. Atorvastatin

**Q5389**: D. Atrahimovich, et al. Punicalagin Decreases Serum Glucose Levels and Increases PON1 Activity and HDL Anti-Inflammatory Values in Balb/c Mice Fed a High-Fat Diet. Oxid Med Cell Longev 2018;2018(2673076

**Agents**: Punicalagin, Quercetin, Atorvastatin **Vehicle**: water, distilled, Tween 80; **Route**: SC; **Species**: Mice; **Pump**: 1004; **Duration**: 28 days;

**ALZET Comments**: Dose (punicalagin 140μg/100 μl, quercetin 42μg/100 μl, atorvastatin 15mg/100 μl); 2% Tween 80 used; Controls received mp w/ vehicle; animal info (male Balb/c mice, 8 weeks old); no stress: Mouse BW was not affected by sc-implanted pump treatments. (see pg. 3);


**Agents**: Atorvastatin calcium **Vehicle**: Route: SC; **Species**: Mice; **Pump**: 2004; **Duration**: 12 weeks;

**ALZET Comments**: Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Male C57BL/6 mice (8 wk old, 18±22 g)); cardiovascular; diabetes; Therapeutic indication (diabetic cardiomyopathy);


**Agents**: Atorvastatin **Vehicle**: DMSO; CSF, artificial; **Route**: CSF/CNS; **Species**: Rat; **Pump**: 1003D; **Duration**: 14 days;

**ALZET Comments**: Controls received mp w/ vehicle; animal info (male, SHRSP/Izm, WKY, 14-16 wksold)

2. Fluvastatin


**Agents**: Fluvastatin **Vehicle**: DMSO, Ringer’s Solution; **Route**: Ear (cochlea); **Species**: Guinea Pig; **Pump**: 2004; **Duration**: 28 days;

**ALZET Comments**: Dose (fluvastatin 50 μM); animal info (Outbred Hartley guinea pigs of both sexes 200–500 g); post op. care (Buprenex); Cannula used;

**P3443**: A. Corsini, et al. Non-lipid-related effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Cardiology 1996;87(458-468

**Agents**: Mevalonate; Fluvastatin **Vehicle**: Saline, physiological; **Route**: IP; perivascular (arterial collar); **Species**: Rabbit; **Pump**: Duration: 5 days;

**ALZET Comments**: tissue perfusion (lesion site-carotid collar); enzyme inhibitor (HMG-CoA reductase)


**Agents**: Mevalonate; Fluvastatin **Vehicle**: Route: IP; perivascular (arterial collar); **Species**: rabbit; **Pump**: Duration: no duration posted;

**ALZET Comments**: controls received mp w/ saline; tissue perfusion (carotid artery collar); cardiovascular; enzyme inhibitor (HMG-CoA reductase)
3. Lovastatin

**Q4310**: M. A. Assaggaf, *et al.* Prevention of Phenytoin-Induced Gingival Overgrowth by Lovastatin in Mice. AMERICAN JOURNAL OF PATHOLOGY 2015;185(1588-1599)

**Agents**: Phenytoin; lovastatin  
**Vehicle**: Water; propylene glycol; ethanol  
**Route**: SC  
**Species**: Mice  
**Pump**: 2002  
**Duration**: 12 weeks;  
**ALZET Comments**: Controls received mp w/ vehicle or saline; animal info (male, BALB/cByJ, 8 weeks old); 9% ethanol used; 41% propylene glycol used; long-term study; phenytoin and lovastatin inside one pump; used autoclips; pumps primed in 37°C saline overinight;


**Agents**: Lovastatin; Pravastatin; Liposomes; Simvastatin  
**Vehicle**: Propylene glycol  
**Route**: Species: Rat  
**Pump**: 2ML4  
**Duration**: no duration posted;  
**ALZET Comments**: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

4. Pravastatin


**Agents**: Pravastatin; Y-27632  
**Vehicle**: DMSO  
**Route**: SC  
**Species**: Mice  
**Pump**: 1002  
**Duration**: 2 weeks;  
**ALZET Comments**: Animal info (female, C57BL6); enzyme inhibitor (ROCK, Rho-associated protein kinase); 10% DMSO used

**P9274**: H. Zaher, *et al.* Targeted disruption of murine organic anion-transporting polypeptide 1b2 (oatp1b2/Slco1b2) significantly alters disposition of prototypical drug substrates pravastatin and rifampin. MOLECULAR PHARMACOLOGY 2008;74(2):320-329

**Agents**: Rifampin; pravastatin  
**Vehicle**: Water; DMSO  
**Route**: SC  
**Species**: Mice  
**Pump**: 2001D  
**Duration**: 24 hours;  
**ALZET Comments**: Functionality of mp verified by plasma concentrations; dose-response (fig. 5); comparison of IV injections vs. mp; animal info (male, DBA1/lacJ, wt, Slco1b2 -/-, 9-14 wks old); 0.5% DMSO used


**Agents**: Lovastatin; Pravastatin; Liposomes; Simvastatin  
**Vehicle**: Propylene glycol  
**Route**: Species: Rat  
**Pump**: 2ML4  
**Duration**: no duration posted;  
**ALZET Comments**: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

5. Rosuvastatin

**Q4414**: P. Escudero, *et al.* Combined treatment with bexarotene and rosuvastatin reduces angiotensin-II-induced abdominal aortic aneurysm in apoE(-/-) mice and angiogenesis. BRITISH JOURNAL OF PHARMACOLOGY 2015;172(2946-2960)

**Agents**: Rosuvastatin, Angiotensin II  
**Vehicle**: Saline  
**Route**: SC  
**Species**: Mice  
**Pump**: 2004  
**Duration**: 5 days;  
**ALZET Comments**: Controls received mp w/ vehicle; animal info (apoE -/-, 8 weeks old); cardiovascular; peptides; “Because the s.c. administration of the statin using an osmotic minipump allows 100% drug bioavailability and its p.o. administration results in 34.5% bioavailability in mice (Peng et al., 2009), we chose the former route to ensure a full dosage effect.” pg 2948; comparison of mp vs. oral gavage
ALZET® Bibliography

Q3875: P. Escudero, et al. Combined Sub-Optimal Doses of Rosuvastatin and Bexarotene Impair Angiotensin II-Induced Arterial Mononuclear Cell Adhesion Through Inhibition of Nox5 Signaling Pathways and Increased RXR/PPARalpha and RXR/PPARgamma Interactions. ANTIOXIDANTS & REDOX SIGNALING 2015;22(9):901-920
Agents: Angiotensin II; Rosuvastatin Vehicle: Saline; Route: SC; Species: Mice; Pump: Duration: 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL6 or ApoE-/-, 23-30g); cardiovascular; peptides; antihypertensive;

Q3783: E. Kilic, et al. HMG-CoA reductase inhibition promotes neurological recovery, peri-lesional tissue remodeling, and contralesional pyramidal tract plasticity after focal cerebral ischemia. Frontiers in Cellular Neuroscience 2014;8(U1-U10
Agents: Rosuvastatin Vehicle: NaCl; Route: CSF/CNS; Species: Mice; Pump: 2004; Duration: 4 weeks;
ALZET Comments: Control animals received mp w/ vehicle; animal info (C57BL6/J, 23-25 g); ALZET brain infusion kit 3 used; enzyme inhibitor (HMG-CoA reductase)

6. Simvastatin

Agents: Simvastatin Vehicle: DMSO; PBS; Route: SC; Species: Mice (nude); Pump: 2006; Duration: ALZET Comments: Dose (11 mg/kg/day); 40% DMSO, 60% PBS used; Controls received mp w/ vehicle; animal info (6 week old male Athymic Nude-Foxn1Nu mice);

Agents: Simvastatin Vehicle: Polyethylene glycol; Route: SC; Species: Rat; Pump: Duration: ALZET Comments: Control animals received mp w/ vehicle; animal info (9 wks old, male, Wistar)

Q0763: P. Wei, et al. Simvastatin Reverses Podocyte Injury but not Mesangial Expansion in Early Stage Type 2 Diabetes Mellitus. RENAL FAILURE 2009;31(6):503-513
Agents: Simvastatin Vehicle: Ethanol; Route: SC; Species: Mice; Pump: Duration: 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL6/6, male, 26 wks old); 60% ethanol used

Agents: Simvastatin Vehicle: CSF/CNS; Species: Rat; Pump: 2004; Duration: 4 weeks;
ALZET Comments: Comparison of PO gavage vs. mp; ALZET brain infusion kit used; post op. care (buprenorphine); animal info (female, Long Evans, adult, 200-22 g.); cannula placement confirmed by preparing cryosections of the brain at the lateral ventricle and verifying the presence of a cavity created by the cannula; spinal cord injury

Agents: Simvastatin Vehicle: PEG 400; Route: SC; bone (femur); Species: Mice; Pump: 1002; Duration: 14 days;
ALZET Comments: Comparison of SC injections vs. SC mp vs. localized delivery; half-life (p. 2 of 6) "about 2 hours in humans"; animal info (mature, male, Balb-C); tissue perfusion (femur); compound passed through sterile filter before filling in pumps; silicone tube used; "continuous systemic delivery resulted in a 160% larger force at failure."; "Continuous local delivery... resulted in a 170% larger force at failure as well as a twofold larger energy uptake."

Agents: Simvastatin Vehicle: Water, distilled; Route: SC; Species: Rat; Pump: Duration: ALZET Comments: Controls received no treatment; animal info (male, Sprague-Dawley, 225-250 g)
Agents: Lovastatin; Pravastatin; Liposomes; Simvastatin Vehicle: Propylene glycol; Route: Species: Rat; Pump: 2ML4; Duration: no duration posted;
ALZET Comments: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

7. Pitavastatin

Agents: Pitavastatin; Wortmannin; Y-27632 Vehicle: DMSO; saline; Route: SC; Species: Rat; Pump: 2ML4; Duration: 7 weeks;
ALZET Comments: Controls received mp w/ vehicle; long-term study; pumps replaced; enzyme inhibitor (phosphatidylinositol 3-kinase, Rho kinase); cardiovascular; multiple pumps per animal (2); animal info (male, Dahl S, Dahl R, 11 wks old); 8% DMSO used