# Supplementary material

Supplementary Table S1: Details of clinical trials design for vamorolone in healthy and Duchenne and Becker muscular dystrophy subjects. In all trials, vamorolone was administered orally as a cherry-flavoured suspension (4% by weight), and in the Phase 2 trials this vamorolone was administered along with 8 oz of whole milk (or equivalent high-fat food portion). \* indicates completed.

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| **Study ID** (NCT Number)  Study title, *Phase*, *Duration* | **Participants** | **Interventions** | **Study objective specific outcome measures** | **Enrolment requirements** |
| **VBP15-001** (NCT02415439)  A Phase 1 SAD and MAD Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of VBP15 in Healthy Adult Subjects  *Phase 1*  *Duration: 2015-16\** | Male healthy adults aged 18-65 yrs (SAD n = 54, MAD n = 32) | **SAD.** 8 groups: single dose VAM (0.1, 0.3, 1, 3, 8, 20 mg/kg) or PBO under fasting conditions or VAM (8 mg/kg) within 30 min of start of high fat/high-calorie meal. Monitored for 4 days.  **MAD.** 4 groups: daily VAM (1, 3, 9, 20 mg/kg/d) or PBO for 2 wks under fasting conditions. | **Primary**  ***Adverse events:*** number of subjects  ***Pharmacokinetics:*** Cmax, AUCInf | **Inclusion**   1. For SAD study: Male subjects, aged 18-65 yrs. 2. For MAD study: Male subjects or female subjects of nonchildbearing, aged 18-65 yrs.   **Exclusion**   1. For MAD Study: Women of childbearing potential. 2. Clinically significant abnormal laboratory parameters |
| **VBP15-002** (NCT02760264)  A Study to Assess Vamorolone in Boys With DMD  *Phase 2A*  *Duration: 2016-18\** | Male DMD aged 4-<7 yrs (steroid naïve; n = 48) | 4 groups: daily VAM (0.25, 0.75, 2, 6 mg/kg/d) for 2 wks with 2-wk washout. | **Primary**  ***Adverse events:*** total number, overall summary (assessed by CTCAE v4.03)  **Secondary**  ***Pharmacokinetics:*** Cmax, Tmax, AUCInf, clearance, t1/2 (serum)  ***Pharmacodynamic biomarkers (serum)***  *Adrenal axis suppression:* first in morning cortisol  *Bone turnover:* osteocalcin, P1NP, CTX-1  *Insulin resistance*: fasting glucose, fasting insulin  ***Metabolites in Safety Testing assessment (serum)***  **Exploratory**  ***Muscle function:*** TTSTAND, TTCLIMB, TTRW, 6MWT, NSAA, QMT | **Inclusion**   1. Guardian consent and willingness to comply 2. DMD diagnosis 3. ≥4-<7 years old at enrolment 4. Complete TTSTAND unassisted 5. Clinical laboratory tests within normal range 6. Evidence of chicken pox immunity   **Exclusion**   1. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 2. Current/ history: chronic systemic fungal or viral infections 3. Acute illness within 4 wks prior to first dose 4. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 5. Evidence of symptomatic cardiomyopathy 6. Current/previous treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos 7. Use of idebenone within 4 wks prior to first dose 8. Allergy/hypersensitivity to drug 9. Severe behavioural or cognitive problems 10. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 11. Current/previous (within 3 mos of start) use of other investigational drug 12. Previous enrolment in VBP15-002. |
| **VBP15-003** (NCT02760277)  An Extension Study to Assess Vamorolone in Boys With DMD  *Phase 2A*  *Duration: 2016-18\** | Male DMD aged 4-7 yrs (steroid naïve; n = 48) | 4 groups: daily VAM (0.25, 0.75, 2, 6 mg/kg/d) for 24 wks (~6 mos) | **Primary**  ***Adverse events:*** number of participants & total number (assessed by CTCAE v4.03)  ***Muscle function:*** TTSTAND velocity  ***Growth:***BMI z-score  **Secondary**  ***Muscle function:*** TTCLIMB, TTRW, 6MWT, NSAA, QMT  ***Pharmacodynamic biomarkers (serum)***  *Adrenal axis suppression:* ACTH  *Bone turnover:* osteocalcin, P1NP, CTX  *Insulin resistance*: HbA1c, fasting glucose, fasting insulin  **Exploratory**  ***Pharmacodynamic biomarkers (serum):*** Extended panel via SomaScan aptamer arrays.  ***Proteomic profiling*** | **Inclusion**   1. Guardian consent and willingness to comply 2. Completion of VBP15-002   **Exclusion**   1. Serious or severe treatment-related adverse event in VBP15-002 2. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 3. Current/ history: chronic systemic fungal or viral infections 4. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 5. Evidence of symptomatic cardiomyopathy 6. Current/previous treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos 7. Use of idebenone within 4 wks prior to first dose 8. Allergy/hypersensitivity to drug 9. Severe behavioural or cognitive problems 10. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 11. Current/previous (within 3 mos of start) use of other investigational drug |
| **VBP15-LTE** (NCT03038399)  Long-term Extension Study to Assess Vamorolone in Boys With DMD  *Phase 2A*  *Duration: 2017-20\** | Male DMD aged 4-7 yrs (steroid naïve; n = 46) | 4 groups: daily VAM (2, 4, 6 mg/kg/d) for 24 mos (2 yrs)  (i, ii) treated with low-dose VAM (0.25 or 0.75 mg/kg/d) in VBP-002/003, increased dosage to 2-6 mg/kg/d.  (iii, iv) treated with high-dose VAM (2 or 6 mg/kg/d) in VBP-002/003, maintained dosage at 2-6 mg/kg/d. | **Primary**  ***Adverse events:*** number of participants & total number (assessed by CTCAE v4.03)  ***Muscle function:*** TTSTAND velocity  ***Growth:***BMI z-score  **Secondary**  ***Muscle function:*** TTCLIMB, TTRW, 6MWT, NSAA, QMT  ***Growth:*** BMI z-score, height z-score  ***Bone health:*** bone age, spine fractures  ***Pharmacodynamic biomarkers (serum)***  *Adrenal axis suppression:* ACTH  *Bone turnover:* osteocalcin, P1NP, CTX  *Insulin resistance*: HbA1c, fasting glucose, fasting insulin  **Exploratory**  ***Muscle function:*** PODCI  ***Pharmacodynamic biomarkers (serum):*** Extended panel  ***DNA testing:*** genetic modifiers of DMD | **Inclusion**   1. Guardian consent and willingness to comply 2. Completion of VBP15-003 up to 24-wk assessments   **Exclusion**   1. Serious or severe treatment-related adverse event in VBP15-003 2. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 3. Current/ history: chronic systemic fungal or viral infections 4. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 5. Evidence of symptomatic cardiomyopathy 6. Current/previous treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos 7. Use of idebenone within 4 wks prior to first dose 8. Allergy/hypersensitivity to drug 9. Severe behavioural or cognitive problems 10. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 11. Current/previous (within 3 mos of start) use of other investigational drug |
| **VBP15-004** (NCT03439670)  A Study to Assess the Efficacy and Safety of Vamorolone in Boys With DMD  *Phase 2B*  *Duration: 2018-21\** | Male DMD aged 4-<7 yrs (steroid naïve; n = 114) | 6 groups: daily VAM (2 or 6 mg/kg/d), PRED (0.75 mg/kg/d), PBO for 48 wks:  (i, ii) VAM for 48 wks,  (iii, iv) PRED for 24 wks, transition for 4 wks, then VAM for 20 wks,  (v, vi) PBO for 24 wks, transition for 4 wks, then VAM for 20 wks. | **Primary**  ***Muscle function:*** TTSTAND velocity (for vamorolone 6 mg/kg/d group vs placebo at 24 wks)  **Secondary**  ***Muscle function:*** TTSTAND, TTCLIMB, TTRW, 6MWT, NSAA, hand-held myometry (knee and elbow extensors), ankle ROM.  ***Pharmacodynamic biomarkers (serum)***  *Adrenal axis suppression:* first in morning cortisol, ACTH stimulation  *Bone turnover:* osteocalcin, CTX  *Insulin resistance*: fasting glucose, fasting insulin  **Exploratory**  ***Muscle function:*** PODCI  ***Behaviour change:*** PARS III  ***Treatment acceptability:*** TSQM, Ease of Study Medication Administration Assessment, blindedness assessment  ***DNA testing:*** genetic modifiers of DMD  ***Pharmacodynamic biomarkers (serum):*** Extended panel | **Inclusion**   1. Guardian consent and willingness to comply 2. DMD diagnosis 3. ≥4-<7 yrs old at enrolment 4. >13-≤39.9 kg at enrolment 5. Walk independently without assistive devices 6. Complete TTSTAND unassisted 7. Clinical laboratory tests within normal range 8. Evidence of chicken pox immunity 9. Able to swallow tablets   **Exclusion**   1. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 2. Current/ history: chronic systemic fungal or viral infections 3. Acute illness within 4 wks prior to first dose 4. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 5. History of primary hyperaldosteronism 6. Evidence of symptomatic cardiomyopathy 7. Current/previous treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos 8. Use of idebenone within 4 wks prior to first dose 9. Allergy/hypersensitivity to drug 10. Severe behavioural or cognitive problems 11. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 12. Use of herbal remedies & supplement that can impact muscle strength/function within 4 wks prior to first dose 13. Use of medication indicated for DMD (incl Exondys51, Translarna) within 3 mos prior to first dose 14. Administered live attenuated vaccine within 14 d prior to the first dose 15. Current/previous (within 3 mos of start) use of other investigational drug 16. Sibling enrolled in any VAM study/EAP 17. Previous enrolment in VBP15-004. |
| **VBP15-006** (NCT05185622)  A Study to Assess Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years With DMD  *Phase 2*  *Duration: 2022-ongoing* | Male DMD aged 2-<4 (steroid naïve) or 7-<18 yrs (steroid naïve or with steroid treatment) | 6 groups: daily VAM (2 or 6 mg/kg/d) for 12 wks:  (i, ii) VAM (2 or 6 mg/kg/d) in males aged 2-<4yrs,  (iii, v) VAM (2 or 6 mg/kg/d) in males aged 7-<18yrs without current steroid treatment,  (iv, vi) VAM (2 or 6 mg/kg/d) in males aged 7-<18yrs with stable steroid treatment. | **Primary**  ***Adverse events:*** number of participants (assessed by CTCAE v4.03)  ***Abnormal clinical features (number of participants):*** cushingoid features, blood chemistry, urinalysis, ECG, glaucoma, cataracts  ***Growth:*** BMI, BMI z-score, height (ulnar length), height z-score, weight  ***Vital signs:*** BP, HR, RR, body temperature  **Secondary**  ***Pharmacokinetics:*** AUCInf (serum; for 7-<18 yrs)  ***Pharmacodynamic biomarkers (serum)***  *Adrenal axis suppression:* first in morning cortisol  *Insulin resistance*: HbA1c, fasting glucose, fasting insulin  **Exploratory**  ***Pharmacodynamic biomarkers (serum)***  *Bone turnover:* osteocalcin, P1NP, CTX-1  ***Muscle function:*** Bayley-III Gross Motor scale (for 2-<4 yrs), PUL test (for 7-<18 yrs), PODCI  ***Behaviour change:*** PARS III  ***Medicine acceptability:*** Ease of Study Medication Administration Assessment (for 2-<4 yrs), Study Medication Acceptability Assessment (for 7-<18 yrs) | **Inclusion**   1. Guardian consent and willingness to comply 2. DMD diagnosis 3. 2-<7 yrs OR 7-<18 yrs old at enrolment 4. If 7-<18 yrs with current standard GC treatment, it has been stable for >3 mos prior to trial commencement 5. If 7-<18 yrs with no current GC treatment, no oral GC for >3 mos prior to trial commencement 6. Clinical laboratory tests within normal range 7. Evidence of chicken pox immunity   **Exclusion**   1. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 2. Current/ history: chronic systemic fungal or viral infections 3. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 4. History of primary hyperaldosteronism 5. Evidence of symptomatic cardiomyopathy 6. If 2-<4 yrs, current/previous treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos 7. Allergy/hypersensitivity to drug 8. Use of idebenone within 4 wks prior to first dose 9. Severe behavioural or cognitive problems 10. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 11. Use of herbal remedies & supplement that can impact muscle strength/function within 4 wks prior to first dose 12. Use of medication indicated for DMD (incl Exondys51, Exondys53, Exondys45, Viltepso, Translarna) within 3 mos prior to first dose 13. Administered live attenuated vaccine within 14 d prior to the first dose 14. Current/previous (within 3 mos of start) use of other investigational drug 15. Previous enrolment in VBP15-006 or other VAM study. |
| **VBP15-EAP** (NCT03863119)  Expanded Access Protocol for Boys with DMD  *Phase N/A*  *Duration: 2019-ongoing* | Male DMD that completed the VBP15-LTE or VBP15-004 | Daily VAM (2, 4, 6 mg/kg/d) ongoing | N/A | **Inclusion**   1. Guardian consent and willingness to comply 2. Completion of VBP15-003 up to 2-yr assessments OR VBP15-004 up to 48-wk assessments   **Exclusion**   1. Serious or severe treatment-related adverse event in VBP15-LTE or VBP15-004 2. Unwilling to comply with medical care and follow-up requirements |
| **VBP15-BMD-001** (NCT05166109)  A Study to Assess Vamorolone in BMD  *Phase 2A*  *Duration: 2022-ongoing* | Male BMD aged 18-64 yrs | 2 groups: daily VAM (500 mg/d or 250 mg if <50 kg body weight), or PBO | **Primary**  ***Adverse events:*** number of participants (assessed by CTCAE v4.03)  ***Growth:*** body weight, height  ***Vital signs:*** BP, HR, RR, body temperature  ***Other clinical (number of participants):*** blood chemistry, urinalysis, ECG  ***Tolerability:*** Premature discontinuation  **Secondary**  ***Pharmacokinetics:*** AUCInf (serum)  ***Pharmacodynamic biomarkers***  *Adrenal axis suppression:* first in morning cortisol (salivary)  *Bone turnover:* osteocalcin (serum)  *Inflammation:* CD23, CCL22 (serum)  *Insulin resistance*: HbA1c, fasting glucose, fasting insulin (serum)  **Exploratory**  ***Muscle function:*** TTRW, NSAA  ***Tolerability:*** NeuroQOL score | **Inclusion**   1. Subject/guardian consent and willingness to comply 2. BMD diagnosis 3. ≥18-<65 yrs old at enrolment 4. Complete TTRW ≤30 s, assistive devices allowed 5. NSAA score ≤32 at screening 6. Clinical laboratory tests within normal range, or if abnormal, not clinically significant 7. No treatment with oral glucocorticoids or other immunosuppressive agents for >3 mos prior to first dose 8. Evidence of chicken pox immunity 9. Willing to use barrier contraceptive method during trial and 30 days post final dose.   **Exclusion**   1. Current/ history: major renal or hepatic impairment, diabetes mellitus or immunosuppression 2. Current/ history: chronic systemic fungal or viral infections 3. Acute illness within 4 wks prior to first dose 4. Use of mineralocorticoid receptor agents within 4 wks prior to first dose 5. Evidence of symptomatic cardiomyopathy 6. Allergy/hypersensitivity to drug 7. Severe behavioural or cognitive problems 8. Previous/ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, full trial completion, or assessment of results. 9. Use of herbal remedies & supplement that can impact muscle strength/function within 4 wks prior to first dose 10. Administered live attenuated vaccine within 14 d prior to the first dose 11. Current/previous (within 3 mos of start) use of other investigational drug 12. Previous enrolment in VBP15-BMD-001 or other VAM study. |
| **Abbreviations:** 6MWT = 6-minute walk test, ACTH = adrenocorticotropic hormone, AUCInf = area under the concentration vs time curve to time infinity, Bayley-III = Bayley Scales of Infant and Toddler Development-III, BL = baseline, BMD = Becker muscular dystrophy, BMI = body mass index, BP = blood pressure, CCL22 = C-C motif chemokine 22 (macrophage-derived chemokine), CD23 = Fc epsilon RII, Cmax = maximum plasma concentration, CTCAE = Common Terminology Criteria for Adverse Events, CTX-1 = C-terminal peptide fragment of collagen 1, DMD = Duchenne muscular dystrophy, ECG = echocardiogram, HbA1c = haemoglobin A1c, HR = heart rate, MAD = multiple ascending dose, NCT = National Clinical Trials, NeuroQol = Quality of Life in Neurological Disorders, NSAA = North Star Ambulatory Assessment, PBO = placebo, P1NP = procollagen 1 N-terminal propeptide, PARS III = Personal Adjustment and Role Skills Scale ed. 3, PODCI = Pediatric Outcome Data Collection Instrument, PRED = prednisone, PUL = Performance of Upper Limb, QMT = Quantitative Muscle Testing, ROM = range of motion, RR = respiratory rate, SAD = single ascending dose, t1/2 = elimination half-life, Tmax = time at maximum plasma concentration, TSQM = Treatment Satisfaction Questionnaire for Medication, TTCLIMB = time to climb test, TTRW = time to run/walk 10 meters test, TTSTAND = time to stand test, VAM = vamorolone/VBP15. | | | | |

Supplementary Table S2: Details of clinical trial results. Summary of published results from completed clinical trials with vamorolone in DMD boys. Results are presented as the effect of vamorolone on outcome measures, compared with (i) untreated DMD or (ii) glucocorticoid-treated DMD (where changes were only for a specific dose level this is clarified in brackets). Beneficial effects indicated by green shading and text. Adverse effects indicated by red shading and text. Mixed effects or no effect indicated by yellow shading and/or black text. Shading in the ‘Measure’ column indicates the effect of vamorolone compared with untreated DMD. All completed clinical trials involved DMD steroid naïve boys aged 4-7 yrs, except for VBP15-001 that used normal adult males aged 19-64 yrs. For design of these clinical trials see summary in Table 1 and/or details in Supplementary Table S1.

| **Study details** | **Results: effects of vamorolone (VAM)** | | |  |
| --- | --- | --- | --- | --- |
| **Study ID:** design, *analyses details* | **Measure** | **i. VAM vs baseline (BL)/steroid naïve/placebo (PBO)** | **ii. VAM vs glucocorticoid (GC)** | **Ref.** |
| **VBP15-001:** Male healthy adults aged 19-64 yrs (n = 86) with i) single dose VAM (0.1, 0.3, 1, 3, 8, 20 mg/kg) or PBO; ii) 2 wks VAM (1, 3, 9, 20 mg/kg/d) or PBO.  **VBP15-002:** Male DMD (steroid naïve) aged 4-<7 yrs (n = 48) with 2 wks VAM (0.25, 0.75, 2, 6 mg/kg/d) and 2-wk washout. | **Pharmacokinetics** |  | VAM ≈ GCs (e.g., PRED) | [42] |
| **VBP15-002:** Male DMD (steroid naïve) aged 4-<7 yrs (n = 48) with 2 wks VAM (0.25, 0.75, 2, 6 mg/kg/d) and 2-wk washout.  *Comparisons: wk2 vs BL, unless specified.* | **Pharmacokinetics** |  | VAM ≈ GCs (e.g., PRED) | [43] |
| **Efficacy** |  |  |  |
| ***Muscle damage*** | No change in CK, ↓ CK at wk4 (VAM2, VAM6). |  |  |
| ***Pharmacodynamic efficacy biomarkers:*** *anti-inflammatory* | ↓ CD23, IL-22BP, MMP-12 (VAM2, VAM6), ↓ CCL22 (VAM6), ↓ IGFBP-2 (VAM all doses).  No change for ITGα1/β1 (VAM all doses) and LTα1/β2 (VAM0.75, VAM2, VAM6).  ↑ CD23, CCL22, IL-22BP, MMP-12, LTα1/β2 (VAM0.25; i.e., not anti-inflammatory). |  |  |
| **Safety** |  |  |  |
| ***Clinical safety*** | No clinically relevant change for laboratory tests: BMI, vital signs, ECG, haematology, biochemistry, lipid profile, urinalysis, liver function (ALT, AST, GLDH, GGT). Liver enzymes ALT and AST elevated as expected for DMD. |  |  |
| ***Adverse events*** | 46 total TEAEs. *Severity (% of subjects):* 54.2% mild, 4.2% moderate, 0% severe. *TEAE relation to VAM (% of subjects):* 0% definitely related, 16.7% possibly/probably related to VAM, 54.2% unrelated/remotely related. 0 SAEs. |  |  |
| ***Adrenal suppression*** | ↑ % of subjects with reduced morning cortisol with increasing dose: 0% for VAM0.25 and VAM0.75, 18.2% for VAM2, 60% for VAM6 |  |  |
| ***Bone turnover*** | ↓ CTX (bone resorption; VAM2, VAM6), ↓ osteocalcin (bone formation; VAM6), ↓ P1NP (bone formation; VAM0.25, VAM2, VAM6) |  |  |
| ***Insulin resistance*** | No change in fasting glucose or insulin (within normal range)*. Pharmacodynamic biomarkers:* ↑ insulin, leptin (VAM0.25), ↑ AFM (VAM2, VAM6). |  |  |
| ***Pharmacodynamic safety biomarkers:*** *other* | ↑ MMP-3, IGFBP-5 (VAM0.25), ↑ AGT (VAM6). |  |  |
| **VBP15-002:** Male DMD (steroid naïve) aged 4-<7 yrs (n = 48) with 2 wks VAM (0.25, 0.75, 2, 6 mg/kg/d) and 2-wk washout.  **VBP15-003:** Male DMD aged 4-7 yrs (n = 48) with 24 wks (~6 mos) VAM (0.25, 0.75, 2, 6 mg/kg/d).  *Exposure-response analysis of change in outcome measures with increasing VAM dosage; changes compared with VBP15-002 BL.* | **Dosage** | Increasing VAM dosage increased effect size on outcome measures: VAM0.25 and VAM0.75 had no significant effect, and VAM2 and VAM6 affected outcome measures. |  | [40] |
| **Efficacy** |  |  |  |
| ***Muscle function*** *(wk 24)* | ↑ TTSTAND velocity, ↓ TTCLIMB time, ↓ TTRW time, ↑ 6MWT distance with increasing VAM dosage. *Sensitivity to VAM dose:* TTSTAND > TTCLIMB > TTRW > 6MWT |  |  |
| ***Pharmacodynamic efficacy biomarkers:*** *anti-inflammatory (wk 2)* | ↓ CD23, CCL22, LTα1/β2, IGFBP-2, MMP-12. *Sensitivity to VAM dose:* IGFBP-2 > CCL22 > IL-22BP > CD23 > LTα1/β2 > MMP-12. |  |  |
| **VBP15-003:** Male DMD aged 4-7 yrs (n = 48) with 24 wks (~6 mos) VAM (0.25, 0.75, 2, 6 mg/kg/d).  *Comparisons: wk24 vs internal: VBP15-002 BL or VAM0.25, or external comparators: steroid naïve DNHS or PRED-treated CINRG.* | **Efficacy** |  |  | [21] |
| ***Muscle function*** *(Δ = change from BL to w24)* | *VAM vs steroid naïve DNHS:* ↑ ΔTTSTAND (VAM2) and ↑ ΔTTRW velocities (VAM6), no difference NSAA.   * *VAM vs VAM0.25:* ↑ ΔTTSTAND (VAM2, VAM6) and ΔTTRW velocities (VAM6), ↑ Δ6MWT distance (VAM2, VAM6), no difference NSAA. |  |  |
| **Safety** |  |  |  |
| ***Clinical safety*** | No clinically relevant change for laboratory tests: vital signs, ECG, haematology, biochemistry, lipid profile, urinalysis, liver function (ALT, AST, GLDH, GGT). Enzymes ALT, AST, CK, and LDH elevated as expected for DMD. |  |  |
| ***Adverse events*** | 42 total TEAEs (87% of subjects), with similar incidence between groups. *Severity (% of subjects):* 50% mild, 33.3% moderate, 4.2% severe (unrelated to VAM), 0% serious. 4 SAEs: 0 related to VAM; 1 moderate, 3 severe. |  |  |
| ***Growth*** | *VAM vs BL:* ↑ BMI z-score (VAM6), no change BMI z-score (VAM0.25, VAM0.75, VAM2)   * *VAM vs VAM0.25:* ↑ ΔBMI z-score (VAM6) | *VAM vs PRED-treated CINRG:* ↓ ΔBMI z-score (VAM0.25, VAM0.75) |  |
| ***Adrenal suppression*** | *VAM vs BL:* ↓ ACTH (VAM0.75, VAM6). ↑ subjects with reduced morning cortisol (< 100 nmol/L) with dose increase (0% for VAM0.25, 8.3% VAM0.75, 41.7% for VAM2, 88.9% for VAM6).   * *VAM vs VAM0.25:* ↓ ACTH (VAM0.75, VAM6). |  |  |
| ***Bone turnover*** | *VAM vs BL:* ↓ CTX (bone resorption; VAM0.75, VAM2, VAM6); no change in osteocalcin (bone formation), P1NP (bone formation). |  |  |
| ***Insulin resistance*** | *VAM vs BL:* ↓ fasting glucose (VAM2, VAM6), ↑ fasting insulin (VAM6; indicates possible insulin resistance), no change in HbA1c (normal range).   * *VAM vs VAM0.25:* ↑ fasting insulin (VAM6; indicates possible insulin resistance), no difference for HbA1c (normal range). |  |  |
| **VBP15-LTE:** Male DMD aged 4-7 yrs (n = 46) with 24 mos VAM (2-6 mg/kg/d) (i.e., total VAM treatment of 30 mos, incl. VBP15-002/003).  *Data for midpoint of VBP15-LTE: total VAM treatment of 18 mos (6 mos VBP15-002/003 and 1 yr VBP15-LTE).*  *Comparisons: VBP15-LTE vs internal BL or external comparators: steroid naïve or GC-treated DNHS, or PRED-treated CINRG* | **Efficacy** |  |  | [41] |
| ***Muscle function*** | *VAM vs BL:* ↑ TTSTAND, TTCLIMB, and TTRW velocities, 6MWT distance, and NSAA score.   * *VAM vs steroid naïve DNHS:* ↑ TTCLIMB and TTRW velocities. |  |  |
| **Safety** |  |  |  |
| ***Adverse events*** | 482 total TEAEs, with similar incidence between groups. *TEAE relation to VAM:* 402 unrelated, 37 remotely related, 29 possibly related, 11 probably related, 3 definitely related to VAM. 3 SAEs (not related to VAM). | *VAM vs GC-treated DNHS:* ↓ incidence for VAM6: 2.6% cushingoid (vs DNHS: 72% DEF, 50% PRED), 13.2% weight gain (vs DNHS: 63% DEF, 67% PRED), 0% behaviour change (vs DNHS: 33% DEF, 30% PRED). |  |
| ***Growth*** | *VAM vs BL:* ↑ height percentile, ↑ BMI z-score.   * *VAM vs steroid naïve DNHS:* no difference for height percentile, ↑ BMI z-score. | *VAM vs GC-treated DNHS:* ↑ height percentile, no difference BMI z-score.  *VAM vs PRED-treated CINRG:* ↑ height percentile, no difference BMI z-score. |  |
| **VBP15-LTE:** Male DMD aged 4-7 yrs (n = 46) with 24 mos VAM (2-6 mg/kg/d) (i.e., total VAM treatment of 30 mos, incl. VBP15-002/003).  *Comparisons: VBP15-LTE vs external comparators: steroid naïve, PRED-treated, or DEF-treated DNHS.* | **Efficacy** |  |  | [44] |
| ***Disease progression*** |  | No significant difference in disease progression measured by TTSTAND, TTRW and TTCLIMB velocities (VAM vs steroid naïve vs PRED vs DEF) |  |
| **VBP15-LTE:** Male DMD aged 4-7 yrs (n = 46) with 24 mos VAM (2-6 mg/kg/d) (i.e., total VAM treatment of 30 mos, incl. VBP15-002/003).  *Comparisons: VBP15-LTE vs external comparators: GC-treated DNHS or GC-treated NSUK Network (for NSAA).*  *Note: efficacy assessed only for participants in ‘high-start’ group^.* | **Efficacy** |  |  | [39] |
| ***Muscle function*** | *VAM vs BL:* no change in TTSTAND, TTCLIMB, and TTRW velocities, 6MWT distance, PODCI score, QMT scores (knee extension and flexion, elbow extension and flexion).   * *Dosage, ‘low-start’ (VAM0.25/0.75) vs ‘high-start’ (VAM2/6):* ↓ TTSTAND and TTCLIMB velocities, and 6MWT distance at 6 mos (i.e., end VBP15-002/003). No difference in TTSTAND, TTCLIMB, TTRW, 6MWT, NSAA at 30 mos for ‘low-start’ and ‘high-start’ groups. | *VAM vs GC:* no difference between trajectories of TTSTAND, TTCLIMB, and TTRW velocities and NSAA scores. |  |
| **Safety** |  |  |  |
| ***Clinical safety*** | No clinically relevant change for laboratory tests: vital signs, ECG, haematology, biochemistry, lipid profile, urinalysis, liver function. |  |  |
| ***Adverse events*** | 87 total TEAEs (100% of subjects). *Severity:* 2 serious (unrelated to VAM) and 1 participant TEAE resulting in discontinuation (moderate muscles weakness). 2 SAEs. |  |  |
| ***Growth*** | *VAM vs BL:* no change in height percentile and BMI z-score | *VAM vs GC-treated DNHS:* ↑ Δ height percentile, no difference in ΔBMI z-score. |  |
| **VBP15-004:** Male DMD aged 4-7 yrs (n = 114) with 48 wks VAM (2, 6 mg/kg/d), or 24 wks PRED (0.75 mg/kg/d) or PBO, 4-wk transition, then 20 wks VAM (2, 6 mg/kg/d).  *Comparisons: wk24 vs BL, PBO, or PRED treatment groups.* | **Efficacy** |  |  | [38] |
| ***Muscle function*** *(Δ = change from BL to w24)* | *VAM vs PBO:* ↑ ΔTTSTAND, ΔTTCLIMB, and ΔTTRW (VAM6 only) velocities, Δ6MWT distance, and ΔNSAA score. No difference for PODCI and handheld myometry. | *VAM vs PRED:* VAM2 ↓ ΔTTCLIMB and ΔTTRW velocities, no difference for ΔTTSTAND velocity, Δ6MWT distance, and ΔNSAA score. VAM6 no difference for ΔTTSTAND, ΔTTCLIMB, and ΔTTRW velocities, Δ6MWT distance, and ΔNSAA score. |  |
| ***Treatment satisfaction*** | No difference for TSQM |  |  |
| **Safety** |  |  |  |
| ***Adverse events*** *(% participants)* | similar incidence of TEAEs between groups (79.3% PBO, 83.3% VAM2, 89.3% VAM6, 83.9% PRED. *Severity:* PRED 1 severe TEAE and 1 discontinuation (behaviour change, possibly related to PRED). VAM2 1 SAE (not related to VAM). |  |  |
| ***Growth*** | *VAM vs BL:* no change in height percentile or BMI z-score. | *VAM vs PRED:* ↑ Δ height percentile (VAM6), no difference ΔBMI z-score. |  |
| ***Adrenal suppression*** | *VAM vs BL:* ↓ morning cortisol (VAM2, VAM6).   * Reduced ACTH-stimulated cortisol (< 500 nmol/L @ 60 mins post-ACTH) in 86% subjects (VAM2) ≈ 95% (VAM6) ≈ 100% (PRED) (vs 20% for PBO) | *VAM vs PRED:* ↑ morning cortisol (VAM2; i.e., reduced adrenal suppression), ↓ morning cortisol (VAM6; i.e., increased adrenal suppression) (Note: *PRED vs BL* ↓ morning cortisol). |  |
| ***Bone turnover*** | *VAM vs BL:* no change for CTX (bone resorption), osteocalcin (bone formation), and P1NP (bone formation). | *VAM vs PRED:* VAM2 ↑ CTX, ↑ osteocalcin, ↑ P1NP. VAM6 ↑ CTX, ↓ osteocalcin, ↓ P1NP (Note: *PRED vs BL* ↓ CTX, osteocalcin, P1NP). |  |
| ***Behaviour change*** | *VAM vs PBO:* ↓ PARS III (VAM6) | *VAM vs PRED:* ↑ PARS III (VAM2) |  |
| **Abbreviations:** 6MWT = 6-minute walk test, AFM = afamin, AGT = angiotensinogen, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BL = baseline, CCL22 = C-C motif chemokine 22 (macrophage-derived chemokine), CD23 = Fc epsilon receptor II, CK = creatine kinase, CINRG = Cooperative International Neuromuscular Research Group study (NCT00110669), DNHS = DMD Natural History Study (NCT00468832), DEF = deflazacort, GC = glucocorticoid, GGT = gamma-glutamyl transferase, GLDH = glutamate dehydrogenase, HbA1c = haemoglobin A1c, IGFBP-2 = insulin-like growth factor binding protein-2, IGFBP-5 = insulin-like growth factor binding protein-5, IL-22BP = interleukin-22 binding protein, ITGα1/β1 = integrin α1β1, LDH = lactate dehydrogenase, LTα1/β2 = lymphotoxin α1/β2, MMP-12 = matrix metalloproteinase 12, MMP-3 = matrix metalloproteinase 3, mos = months, NCT = National Clinical Trials, NSAA = North Star Ambulatory Assessment, NSUK = NorthStar United Kingdom, PARS III = Personal Adjustment and Role Skills Scale ed. 3, PBO = placebo, PODCI = Pediatric Outcomes Data Collection Instrument, PRED = prednisone, QMT = Quantitative Muscle Testing, SAEs = serious adverse effects, TEAEs = treatment-emergent adverse effects, TSQM = Treatment Satisfaction Questionnaire for Medication, TTCLIMB = time to climb test, TTRW = time to run/walk 10 meters test, TTSTAND = time to stand test, VAM = vamorolone, VAM0.25/0.75/2/6 = vamorolone 0.25/0.75/2/6 mg/kg/d treatment, wks = weeks, yrs = years.  ^ ‘High-start’ refers to groups in VBP15-002/003/LTE that received VAM2 or VAM6 for full 30 mos (n = 23). ‘Low-start’ refers to groups in VBP15-002/003 with 6 mos VAM0.25 or VAM0.75 and received increased dosage in VBP15-LTE of VAM2 or VAM6 for remaining 24 mos. | | | | |

Supplementary Table S3: Details of pre-clinical studies and results for *in vivo* vamorolone/VBP15 (and other glucocorticoids) compared with vehicle control, in rodent models of A) muscular dystrophy and B) other disorders.

| **Disorder** | **Study details** | **Results of vamorolone and glucocorticoid treatment, compared with vehicle control** | **Ref.** |
| --- | --- | --- | --- |
| ***A. Muscular dystrophies*** | | | |
| DMD | **Trial 1:** 8-wk *mdx* treated with ANEC(5 mg/kg/d) or PRED (1 mg/kg/d) via daily syrup for 3 wks.  **Trial 2:** 8-wk *mdx* untreated or treated with ANEC(40 mg/kg/d) or PRED (5 mg/kg/d) via food for 4 mos. | **Beneficial:**  ***Inflammation:*** ANEC ↓ FL (cathepsin) (ANEC ≈ PRED)  ***Function:*** ANEC ↑ EDL max force (PRED ≈ VEH)  **Adverse:**  ***Growth & atrophy:*** PRED ↓ body mass (ANEC ≈ VEH)  ***Immune:*** PRED ↓ spleen mass (ANEC ≈ VEH) | [68] |
| DMD | **Trial 1:** 2-wk WT and *mdx* mice treated with VAM (5, 15, 30 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 6 wks.  **Trial 2:** 6-wk WT and *mdx* mice treated with VAM (5, 15, 45 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 4 mos., with 2×wkly horizontal treadmill running (30 min @ 12 m/min). | **Beneficial:**  ***Inflammation:*** VAM ↓ HL (cathepsin) (VAM ≈ PRED\*), ↓ diaphragm infiltrate (PRED ≈ VEH)  ***Function:*** VAM ↑ HL and FL grip strength (VAM ≈ PRED\*), ↑ EDL muscle specific force (PRED ≈ VEH), ↓ EDL eccentric contraction-induced force loss (PRED ≈ VEH)  ***Immune:*** ↓ spleen mass (VAM ≈ PRED, to WT-level), ↓ leukocytes (VAM ≈ PRED, to WT-level)  **Adverse:**  ***Growth & atrophy:*** PRED ↓ body and tibia length (VAM ≈ VEH)  ***Pathology severity:*** PRED ↑ gastrocnemius degenerating myofibres, fibrosis (VAM ≈ VEH)  ***Immune:*** PRED ↓ T cell counts and activation (i.e., immunosuppression; VAM ≈ VEH)  ***Cardiac:*** PRED ↑ heart mass, fibrosis (VAM ≈ VEH)  ***Other:*** PRED ↓ bone density: trabecular thickness (VAM ≈ VEH) | [20] |
| DMD | *Archival gastrocnemius samples from Heier et al. [20] (above).*  6-wk WT and *mdx* mice treated with VAM (15 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 4 mos., with 2×wkly horizontal treadmill running (30 min @ 12 m/min). | **Beneficial:**  ***Inflammation:*** VAM ↓ TGF-β and fibrosis pathways (VAM ≈ PRED) | [10] |
| DMD | *Archival diaphragm samples from Heier et al. [20] (above):*  **Trial 1:** 2-wk WT and *mdx* mice treated with VAM (15 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 6 wks.  **Trial 2:** 6-wk WT and *mdx* mice treated with VAM (45 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 4 mos., with 2×wkly horizontal treadmill running (30 min @ 12 m/min). | **Beneficial:**  ***Inflammation:*** VAM ↓ inflammatory miRNAs (VAM ≈ PRED)  **Adverse:**  ***Metabolic:*** PRED ↑ insulin resistance miRNAs (VAM ≈ VEH)  ***Cardiac:*** PRED ↑ hypertension miRNAs (VAM ≈ VEH)  ***Other:*** PRED ↑ adrenal suppression, behaviour issues miRNAs (VAM ≈ VEH) | [48] |
| DMD | **Trial 1 (MR antagonism):** 3-mos WT and *mdx* mice pre-treated with VAM (20 mg/kg/d), eplerenone (100 mg/kg/d), spironolactone (20 mg/kg/d), or VEH via daily CS for 1 wk, then aldosterone (0.25 mg/kg/d; MR agonist) or VEH via osmotic pump for 6 wks.  **Trial 2:** *Archival heart samples from Heier et al. [20].* 6-wk WT and *mdx* mice treated with VAM (45 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily (AM) CS for 4 mos., with 2×wkly horizontal treadmill running (30 min @ 12 m/min).  **Trial 3:** 2-mos DBA/2J (D2)-*mdx* mice treated with VAM (30 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily CS for 8 wks. | **Beneficial:**  ***Cardiac:*** VAM ↓ *mdx* (+ aldosterone) hypertension & cardiomyopathy (VAM ≈ eplerenone & spironolactone), ↑ D2-*mdx* cardiac function (fractional shortening; PRED ≈ VAM)  ***Other:*** MR antagonist: ↓ *mdx* (+ aldosterone) kidney size (VAM ≈ eplerenone & spironolactone)  **Adverse:**  ***Metabolic:*** PRED ↑ D2-*mdx* serum insulin (VAM ≈ VEH)  ***Cardiac:*** PRED ↑ D2-*mdx* heart mass, left ventricular volume (VAM ≈ VEH)  ***Other:*** PRED MR agonist: ↑ *mdx* MR & GR side effect pathway miRNAs (VAM ≈ VEH) | [46] |
| DMD | 4-wk *mdx* mice treated for 4 wks with VAM (30 mg/kg/d), PRED (5 mg/kg/d), or VEH via daily CS, or β-aminoisobutyric acid (100, 500 mg/kg/d) via drinking water, or rituximab (1 mg/kg) via single injection at the start of trial period, or a combination of treatments. | **Beneficial:**  ***Inflammation:*** VAM ↓ NF-κB and TGFβ fibrosis cascades (VAM shared many PRED-responsive biomarkers) | [47] |
| Dysferlinopathy | 12-wk SJL/J untreated or treated with ANEC(40 mg/kg/d) or PRED (5 mg/kg/d) via food for 4 mos. | **Beneficial:**  ***Growth & atrophy:*** ANEC ↑ body mass (PRED ≈ VEH)  ***Pathology severity:*** ANEC ↓ central nuclei (PRED ≈ VEH; muscle not specified)  ***Function:*** ANEC ↑ FL grip strength, motor coordination (PRED ≈ VEH)  ***Other:*** ANEC ↓ HL and FL dye-uptake after injury (FL: ANEC ≈ PRED; HL: PRED ≈ VEH)  **Adverse:**  ***Immune:*** PRED ↓ spleen mass (ANEC ≈ VEH)  ***Cardiac:*** PRED ↑ heart mass (ANEC ≈ VEH) | [68] |
| Dysferlinopathy | 7-mos WT and BLAJ mice treated with VAM (30 mg/kg), PRED (30 mg/kg), or VEH via CS for 5 doses over 3 days (acute, a) or daily for 3 mos. (chronic, c). | **Beneficial:**  ***Pathology severity:*** VAM ↓ adipogenic replacement of myofibres in gastrocnemius (perilipin-1-postive foci; PRED ≈ VEH)  ***Inflammation:*** VAM ↓ gastrocnemius inflammatory CD209 and IRF7 gene expression  ***Function:*** VAM ↑ HL grip strength (FL: VAM ≈ VEH), ↓ EDL eccentric contraction-induced force loss (PRED ≈ VEH)  ***Other:*** VAM ↑ myofibre repair following laser-injury (a), ↑ biceps myofibre repair following laser-injury (not PRED, see **Adverse**), ↓ *ex vivo* EDL eccentric contraction-induced muscle injury, *in vivo* gastrocnemius myofibre injury (not PRED, see **Adverse**)  **Adverse:**  ***Growth & atrophy:*** PRED ↑ gastrocnemius atrophy: ↑ myofibre loss, ↓ myofibre CSA (VAM ≈ VEH)  ***Function:*** PRED ↓ HL and FL grip strength  ***Other:*** PRED ↓ biceps myofibre repair following laser-injury, ↑ *in vivo* gastrocnemius myofibre injury | [49] |
| ***B. Other disorders*** | | | |
| Allergic lung inflammation | 6-wk BALB/c mice underwent ovalbumin-induced lung inflammation (day 0), at 7 wks (day 6) treated with VAM (20 mg/kg/d), PRED (5 mg/kg/d), or VEH via CS for 6 days. | **Beneficial:**  ***Inflammation:*** VAM ↓ infiltrating eosinophils, T cells, inflammatory foci, cytokine IL-13, chemokine RANTES (VAM ≈ PRED)  **Adverse:**  ***Growth & atrophy:*** PRED ↓ tibia length (VAM ≈ VEH) | [50] |
| Brain tumour (glioma) | **Trial 1:** 2-day (P2) J;Nu mice injected with brainstem glioma cells, 8 days post-injection mice treated with VAM (30 mg/kg/d), DEX (2.4 mg/kg/d), or VEH via daily CS for 15 wks.  **Trial 2:** 3-wk NOD *SCID* mice injected with PKC-L tumour cells and treated with VAM (30 mg/kg/d), dexamethasone (2.4 mg/kg/d), or VEH via daily CS for 2 wks. | **Beneficial:**  ***Pathology severity:*** VAM ↑ NOD *SCID* mouse activity (VAM ≈ DEX) & survival (PRED ≈ VEH)  **Adverse:**  ***Growth & atrophy:*** VAM ↓ J:Nu tibia length (VAM ≈ DEX). DEX ↓ body length (VAM ≈ VEH)  ***Immune:*** VAM ↓ J:Nu spleen length (VAM > DEX length) & mass (VAM ≈ DEX) | [51] |
| Critical illness myopathy | Adult Sprague-Dawley rats under intensive care unit conditions (i.e., sedation, immobilisation, and mechanical ventilation) treated with VAM (5 mg/kg/d), PRED (20 mg/kg/d), or VEH via CS for 5 days. | **Beneficial:**  ***Growth & atrophy:*** VAM ↓ body mass loss (PRED ≈ VEH), ↓ soleus atrophy (mass loss, myofibre CSA) (VAM ≈ PRED), ↓ soleus atrogenes: ↓ MuRF1, no change atrogin‐1 (not PRED, see **Adverse**)  ***Pathology severity:*** VAM ↑ rat survival (PRED ≈ VEH)  ***Function:*** VAM ↑ soleus myofibre max. force (VAM ≈ PRED)  **Adverse:**  ***Growth & atrophy:*** PRED ↑ EDL atrophy (mass loss, myofibre CSA), ↑ soleus atrogene: MuRF1  ***Pathology severity:*** PRED ↑ soleus calpain-1 levels (VAM ≈ VEH)  ***Immune:*** PRED ↑ serum cytokines (IL‐18, fractalkine, IP‐10) (VAM ≈ VEH)  ***Function:*** PRED ↓ EDL myofibre max. and specific force (VAM ≈ VEH) | [52]\* |
| Inflammatory bowel diseases (ulcerative colitis, Crohn’s disease) | **Trial 1:** 8-wk BALB/c mice treated with VAM (30 mg/kg/d), PRED (30 mg/kg/d), or VEH via CS for 3 days, colitis induced by trinitrobenzene sulfonic acid on day 1, sampling on day 4.  **Trial 2:** 12-day CD-1 mice treated with VAM (10, 30, 45 mg/kg/d), PRED (10 mg/kg/d), or VEH via CS for 5 wks. | **Beneficial:**  ***Growth:*** VAM ↓ BALB/c weight loss (PRED ≈ VEH)  ***Pathology severity:*** VAM ↑ BALB/c mouse survival (VAM > PRED > VEH), ↓ BALB/c colitis disease score (PRED ≈ VEH)  **Adverse:**  ***Growth & atrophy:*** VAM 45 mg/kg ↓ CD-1 body length & mass (VAM 45 mg/kg ≈ PRED; VAM 10 mg/kg ≈ VAM 30 mg/kg ≈ VEH) | [53] |
| Multiple sclerosis (experimental autoimmune encephalomyelitis; EAE) | **Trial 1:** 8-wk C57BL/6 mice treated with VAM (30 mg/kg/d), PRED (15 mg/kg/d), or VEH via CS for 21 days, with EAE induced by MOG33-55 peptide-immunisation on day 1.  **Trial 2:** 12-day CD-1 mice treated with VAM (30 mg/kg/d), PRED (10 mg/kg/d), or VEH via CS for 5 wks. | **Beneficial:**  ***Pathology severity:*** VAM ↓ C57BL/6 EAE severity and incidence (VAM ≈ PRED)  ***Inflammation:*** VAM ↓ C57BL/6 spinal cord inflammatory foci (H&E) and cytokines (VAM ≈ PRED)  **Adverse:**  ***Growth & atrophy:*** PRED ↑ CD-1 gastrocnemius atrogene: FBX032 (VAM ≈ VEH), ↓ CD-1 diaphragm mass (VAM ≈ VEH) | [54] |
| Rheumatoid arthritis | 6-8-wk DBA1/J mice underwent collagen antibody‑induced arthritis procedure (day 0-3), from day 7 mice treated with VAM (10, 20, 40 mg/kg/d), PRED (10, 20, 40 mg/kg/d), or VEH via CS for 7 days. | **Beneficial:**  ***Pathology severity:*** VAM 40 mg/kg ↓ disease score (VAM 40 mg/kg ≈ PRED all doses; VAM 10 mg/kg, 20 mg/kg ≈ PRED ≈ VEH), VAM ↓ cartilage destruction (VAM all doses ≈ PRED 10 mg/kg; PRED 20 mg/kg, 40 mg/kg ≈ VEH), VAM 20 mg/kg ↓ bone erosion (VAM 10 mg/kg, 40 mg/kg ≈ PRED ≈ VEH)  ***Inflammation:*** VAM 40 mg/kg ↓ joint inflammation (VAM 40 mg/kg ≈ PRED all doses; VAM 10 mg/kg, 40 mg/kg ≈ VEH), VAM ↓ pro‑inflammatory cytokines: IL-6 (VAM all doses ≈ PRED 20 mg/kg; PRED 10 mg/kg, 40 mg/kg ≈ VEH) | [55] |
| Sickle cell disease (SCD) | 8-12-wk Townes SCD mice treated with VAM (30 mg/kg/d), PRED (30 mg/kg/d), or VEH via CS for 6 wks. | **Beneficial:**  ***Inflammation:*** VAM ↓ liver infiltrate (VAM < PRED, i.e., PRED more effective)  ***Immune:*** VAM ↓ leukocytes & lymphocytes (VAM ≈ PRED)  **Adverse:**  ***Pathology severity:*** VAM ↑ liver necrosis (PRED ≈ VEH),  ***Function:*** VAM ↓ liver function: ↑ plasma aspartate aminotransferase & alkaline phosphatase levels (VAM ≈ PRED)  ***Immune:*** PRED ↓ spleen mass (VAM ≈ VEH) | [56] |
| **Abbreviations:** AM = morning, ANEC = anecortave (VBP1 pro-drug), CSA = cross sectional area, CS = cherry syrup, DEX = dexamethasone, DMD = Duchenne muscular dystrophy, EAE = experimental autoimmune encephalomyelitis, EDL = extensor digitorum longus, FL = forelimb, GR = glucocorticoid receptor, H&E = haematoxylin and eosin, HL = hindlimb, mos. = months, max. = maximum, MR = mineralocorticoid receptor, NCT = National Clinical Trials, NF-κB = nuclear factor kappa B, PKC-L = PDGFβ, H3 K27M, P53 loss-luciferase, PRED = prednisolone/prednisone, SCD = sickle cell disease, TGF-β = transforming growth factor beta, VAM = vamorolone/VBP15, VEH = vehicle, wk = week, WT = wild-type.  \* no statistics reported | | | |