NKR 44: Altitretinoin for hand eczema

Characteristics of studies

Characteristics of included studies

Bissonnette 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention 1 ● *Age (mean)*: 49 ● *sex (%male)*: 71.4 Intervention 2 ● *Age (mean)*: 52 ● *sex (%male)*: 51 Placebo ● *Age (mean)*: 50,4 ● *sex (%male)*: 51 **Included criteria:** Patients eligible for the retreatmenttrial were male patients, and female patients either of non-childbearing potential or of childbearing potential and using appropriate contraception, who participated in the BACH study (aged 18–75 years and diagnosed with severe CHE of at least 6 months' duration and refractory to standard therapy.) and were responders (rated as 'clear' or 'almost clear'hands according to the PGA at treatment end), and who relapsed within 24 weeks after the end of treatment. Relapsewas defined as a modified Total Lesion Symptom Score (mTLSS)‡75% that of baseline in the BACH trial. The mTLSSis a composite measure of the intensity of seven individualCHE symptoms: erythema, scaling, lichenification/hyperkera-tosis, vesiculation, oedema, fissures and pruritus/pain, scoredfrom 0 to 3. Scores are summed, with a maximum value of21 (most severe disease) and a minimum of 0 (no signs or symptoms). **Excluded criteria:** Patients were excluded if they had alanine aminotransferaseand/or aspartate aminotransferase > 250% of the upper limitof normal, triglycerides > 200% of the upper limit of normal,cholesterol or low-density lipoprotein cholesterol > 200% ofthe upper limit of normal, haemoglobin below the lower limitof normal, a score of 20 or higher on the Centre for EpidemiologicalStudies Depression Scale (CES-D), or a history ofmajor psychiatric disorders. Other exclusion criteria weretreatment with other investigational drugs within the previous2 months, or UVB phototherapy, psoralen plus UVA orX-rays, or systemic corticosteroids, retinoids or immunosuppressantswithin the previous 4 weeks, or drugs with thepotential for drug–drug interactions (such as systemic azoles,erythromycin or clarithromycin, simvastatin or St John's wort)within the previous 2 weeks, concomitant retinoids (oral, ortopical to hands) or vitamin supplements containing> 2000 IU vitamin A, known hypersensitivity to retinoids orto any component of the study drug formulation, or knownimmunosuppression. **Pretreatment:** More males in alitrtinoin 10 mg GroupMore with hyperkeratotic HE in the Alitretinoin Groups
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: This was a double-blind, placebo-controlled, randomizedstudy that included 117 patients who achieved 'clear' or'almost clear' hands following initial treatment in the BACH study and relapsed within a 24-week observation period.During the relapse observation period of the BACH study no active treatment of CHE was allowed: only bland emollients were used. Patients who participated in the BACH study had severe disease at baseline according to the Physician's Global Assessment (PGA) persisting for at least 6 months after initial diagnosis and were un responsive to standard therapy including the most potent topical corticosteroids. ● *Dose*: 10 mg ● *Duration*: 12-24 weeks depending of treatment response Intervention 2 ● *Description*: This was a double-blind, placebo-controlled, randomizedstudy that included 117 patients who achieved 'clear' or'almost clear' hands following initial treatment in the BACH study and relapsed within a 24-week observation period.During the relapse observation period of the BACH study no active treatment of CHE was allowed: only bland emollients were used. Patients who participated in the BACH study had severe disease at baseline according to the Physician's Global Assessment (PGA) persisting for at least 6 months after initial diagnosis and were un responsive to standard therapy including the most potent topical corticosteroids. ● *Dose*: 30 mg ● *Duration*: 12-24 weeks depending of treatment response Placebo ● *Description*: This was a double-blind, placebo-controlled, randomizedstudy that included 117 patients who achieved 'clear' or'almost clear' hands following initial treatment in the BACH study and relapsed within a 24-week observation period.During the relapse observation period of the BACH study no active treatment of CHE was allowed: only bland emollients were used. Patients who participated in the BACH study had severe disease at baseline according to the Physician's Global Assessment (PGA) persisting for at least 6 months after initial diagnosis and were un responsive to standard therapy including the most potent topical corticosteroids. ● *Dose*: - ● *Duration*: 12-24 weeks depending of treatment response
Outcomes	*Livskvalitet* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported ● **Scale**: DLQI ● **Range**: 0-30 ● **Direction**: Lower is better ● **Data value**: Endpoint *Hyperkolesterolæmi* ● **Outcome type**: DichotomousOutcome

	● **Reporting**: Fully reported ● **Scale**: >7.77 mmol/L ● **Unit of measure**: mmol/L ● **Direction**: Lower is better ● **Data value**: Endpoint *Hypothyroidisme (low thyroxine)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: <8.3pmol/L ● **Unit of measure**: pmol/L ● **Direction**: Higher is better ● **Data value**: Endpoint ● **Notes**: <8.3 pmol/L (age=<65years) or <8.0 pmol/L (age>65 years) *Hypothyroidisme (high TSH)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: >7.4mU/L ● **Unit of measure**: mU/L ● **Direction**: Lower is better ● **Data value**: Endpoint ● **Notes**: >7.4mU/L (age=< 20 years) or 6.3mU/L (age>20 years) *Hypothyroidisme (TSH low)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: 0.6 mU/L ● **Unit of measure**: mU/L ● **Direction**: Higher is better ● **Data value**: Endpoint ● **Notes**: 0.6 mU/L (age <=20 years) or 0.3 mU/L (age>20 years) *Sværhedsgrad af eksem (10 mg)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: clear/allmost clear ● **Direction**: Higher is better ● **Data value**: Endpoint *Sværhedsgrad af eksemet (30 mg)* ● **Outcome type**: DichotomousOutcome ● **Scale**: clear/allmost clear ● **Direction**: Higher is better ● **Data value**: Endpoint *Hovedpine* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Psykose* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Not reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Autors are employees or consultants for Basilea Pharmaceutical international **Country:** Switzerland, Germany, France, Canada **Setting:** The trial was carried out in patients who responded to initial treatment in the large phase III BACH (Benefit of Alitretinoin in Chronic HandEczema) study7 and relapsed within 24 weeks **Comments:** - **Authors name:** Robert Bissonnette **Institution:** Klinik für Dermatologie, Campus Charite´Mitte Universitats klinik der Humboldt-Universitat, Berlin, Germany **Email:** rbissonnette@innovaderm.ca **Address:** Innovaderm Research Inc., 1851 Rue Sherbrooke E., Suite 502, Montreal, QC H2K 4L5, Canada
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Judgement Comment: antager at det følger samme princip som BACH studiet
Allocation concealment	Low risk	Judgement Comment: antager at det er det samme som i BACH studiet, som dette studie er en efterfølger til
Blinding of participants and personnel	Low risk	Judgement Comment: the placebo and the active drug were indistinguishable and packaged in the same way
Blinding of outcome assessors	Low risk	Judgement Comment: doble blinded
Incomplete outcome data	Low risk	Judgement Comment: As shown in Figure 1, 24 patients (20Æ5%) were withdrawnfrom treatment. The primary reason for withdrawal in the placeboarm was insufficient therapeutic response (n = 8, 17%).In the active arms, three patients withdrew due to adverseevents, three patients withdrew consent and two patients inthe 30 mg group withdrew due to insufficient therapeuticeffect.

Selective outcome reporting	Low risk	Judgement Comment: no protocol, but the published report include all expected outcomes
Other sources of bias	High risk	Judgement Comment: most of the patients had hyperkeratotic hand eczema. Maybe Alitretinoin Works better in hyperkeratotic HE than i nthe other subtypes? Som of the investigators are employed in Basilea Pharmaceutica

Fowler 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age (mean)*: 47.1 ● *sex (%male)*: 65.4 Placebo ● *Age (mean)*: 47.5 ● *sex (%male)*: 50 **Included criteria:** patients with severe chronic hand eczema refractory to very potent topical corticosteroids **Excluded criteria:** on page 1199håndeksem kontrolleres på lokalbehandling, men udbrud ved stopdesuden ACD, psoriasis, AD med behov for behandling, akut dyshydroisk eksem eller kontaktdermatitis, infektion på hænder, psykisk sgd, høretab eller øresgd i anamnesen **Pretreatment:** none
Interventions	**Intervention Characteristics** Intervention ● *Description*: run in consisted of =<16 weeks treatment with very potent TCS fir >= 2 weeksor as indicated by the label. patients were considered to have refractory disease and were randomized to trail treatment if they had sCHE after >= 2weeks of treatment with very potent TCS or at eny later time during run-in. patients with refractory sCHE were randomized to receive alitretinoin 30 mg once daily for <= 24 weeks. pt with sCHE after 12 weeks of treatment were withdrawn ● *Dose*: 30 mg ● *Duration*: 12-24 weeks Placebo ● *Description*: run in consisted of =<16 weeks treatment with very potent TCS fir >= 2 weeksor as indicated by the label. patients were considered to have refractory disease and were randomized to trail treatment if they had sCHE after >= 2weeks of treatment with very potent TCS or at eny later time during run-in. patients with refractory sCHE were randomized to receive placebo once daily for <= 24 weeks. ● *Dose*: - ● *Duration*: 12-24 weeks
Outcomes	*Sværhedsgrad af eksemet* ● **Outcome type**: DichotomousOutcome *Hovedpine* ● **Outcome type**: DichotomousOutcome ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** GSK and also Bayer, Galderma, Innocutis, Quinnova **Country:** USA **Setting:** 7 centres **Comments:** - **Authors name:** Joseph F. Fowler **Institution:** Division of Dermatology, University of Louiseville **Email:** fowlerjoe@msn.com **Address:** Division of Dermatology, University of Louisville, Louisville, KY
Notes	*Charlotte Mortz* on 21/04/2016 04:01 **Outcomes** .

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	
Allocation concealment	Low risk	
Blinding of participants and personnel	Low risk	Judgement Comment: Double blinded. Mht investigators, study personnel, patients, and statisticians were unaware of assigned study treatment. Double blinded. Mht investigators, study personnel, patients, and statisticians were unaware of assigned study treatment.
Blinding of outcome assessors	Low risk	
Incomplete outcome data	Low risk	Judgement Comment: intention-to-treat analyse lavet
Selective outcome reporting	Low risk	
Other sources of bias	High risk	fonded af GSK som producerer alitretinoin

Ruzicka 2004

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention 1 ● *Age (mean)*: 48.7 ● *sex (%male)*: 70 Intervention 2 ● *Age (mean)*: 46.7 ● *sex (%male)*: 74 Intervention 3 ● *Age (mean)*: 48.7 ● *sex (%male)*: 80 Placebo ● *Age (mean)*: 48.7 ● *sex (%male)*: 72 **Included criteria:** Patients were eligible for enrollment in this study if they wereaged 18 to 70 years and diagnosed as having “moderate” or “severe”CHaD (see “Efficacy Assessments”) of at least 3 months’duration and refractory to standard therapy. Refractory statuswas defined as no response, or transient response to at least 4weeks of topical corticosteroids, or intolerance to this regimen.Enrollment was open to patients with all types of chronichand dermatitis, including hyperkeratotic, dyshidrotic (pompholyx),or fingertip dermatitis. Plantar involvement was neitherrequired nor evaluated. Investigators were required to ruleout alternative diagnoses, including infectious dermatoses orpalmar psoriasis. Patients were also required to be either maleor postmenopausal or surgically sterile female. **Excluded criteria:** Patients were excluded from the study if they had activeatopic dermatitis or unequivocal psoriasis not limited to thehands and requiring medicated treatment at the time of enroll-ment. Patients were also excluded if they had significant ab-normalities in liver function (alanine aminotransferase and/oraspartate aminotransferase150% of the upper limit of nor-mal); triglyceridemia (250% of the upper limit of normal);cholesterolemia (150% of the upper limit of normal); a his-tory of psychiatric disorders; active bacterial, fungal, or viralinfection of the hands; clinically relevant allergic contact der-matitis of the hands and were unable to avoid exposure to theallergen; or any other skin disease likely to interfere with theconduct of the study. Other exclusion criteria comprised treat-ment with other investigational drugs within the previous 2months; phototherapy (UV-B, psoralen–UV-A, or x-rays) or useof systemic corticosteroids, retinoids, or immunosuppres-sants within the previous 4 weeks; use of systemic ketocona-zole, itraconazole, erythromycin, or clarithromycin within theprevious 2 weeks; or concomitant use of retinoids (oral or topi-cal) or vitamin supplements containing vitamin A (retinol).Known hypersensitivity to retinoids or to any component of the study drug formulations or known immunosuppression werealso exclusion criteria **Pretreatment:** Patients in each group had similar demographic anddisease characteristics
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Treatment with alitretinoin (BAL4079; Ba-silea Pharmaceutica Ltd) at 10 mgwas given orally once daily after breakfast for 12 weeks, and no dose re-ductions were allowed. All patients were given an emollient (Bep-anthol hand ointment; F. Hoffmann-La Roche Ltd, Basel) withinstructions to apply it as frequently as required ● *Dose*: 10 mg/d ● *Duration*: 12 weeks Intervention 2 ● *Description*: Alitretinoin 20 mg/d, fugtighedscreme ● *Dose*: 20 mg/d ● *Duration*: 12 weeks Intervention 3 ● *Description*: Alitretinoin 40 mg/d, fugtighedscreme ● *Dose*: 40 mg/d ● *Duration*: 12 weeks Placebo ● *Description*: placebo kapsel Fugtighedscreme ● *Dose*: 0 ● *Duration*: 12 weeks
Outcomes	*Livskvalitet* ● **Outcome type**: ContinuousOutcome *Hyperkolesterolæmi* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (low thyroxine)* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (high TSH)* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (TSH low)* ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksem (10 mg)* ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksemet (30 mg)* ● **Outcome type**: DichotomousOutcome *Hovedpine* ● **Outcome type**: DichotomousOutcome

	Psykose ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksemet* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: PGA ● **Range**: 0-4 ● **Direction**: Higher is better ● **Notes**: Reported as clear/ allmost clear
Identification	**Sponsorship source:** Basilea Pharmaceutica **Country:** Switzerland **Setting:** Multicenter ambulant hospital **Comments:** - **Authors name:** Dr Thomas Ruzicka **Institution:** Dep of dermatology Heinrich-Heine University Hospital **Email:** ruzicka@uni-duesseldorf.de **Address:** Heinrich-Heine University Hospital Dusseldorf, Moorenstr 5 40221 Dusseldorf, germany
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Judgement Comment: Eligible patients were randomized to treatment by center, inblocks of 4 without stratification, by use of computergeneratedrandomization codes provided by the study sponsor(Basilea Pharmaceutica Ltd, Basel, Switzerland)
Allocation concealment	Low risk	Judgement Comment: computer- generated randomization codes provided by the study spon- sor (Basilea Pharmaceutica Ltd, Basel, Switzerland)
Blinding of participants and personnel	Low risk	Judgement Comment: incorporatedinto double-blind coded drug packaging. Placebo andactive drug (as soft gelatin capsules) and packaging were indistinguishable
Blinding of outcome assessors	Low risk	Judgement Comment: incorporatedinto double-blind coded drug packaging. Placebo andactive drug (as soft gelatin capsules) and packaging were indistinguishable
Incomplete outcome data	Low risk	
Selective outcome reporting	High risk	Judgement Comment: Der er flest patienter i studiet med hyperkeratotisk håndeksem. Det er dem, der responderer bedst på behandlingen. Det adresseres ikke i diskussionen at visse eksemtyper har forskelligt respons.DLQI værdier rapporteres ikke.Kun ingen signifikant forskel i outcome
Other sources of bias	High risk	several autors are employed in Basilea Parm.

Ruzicka 2008

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention 1 ● *Age (mean)*: 48 ● *sex (%male)*: 55 Intervention 2 ● *Age (mean)*: 47 ● *sex (%male)*: 57 Placebo ● *Age (mean)*: 48 ● *sex (%male)*: 59 **Included criteria:** Patients were eligible for enrolment in this study if they wereaged 18–75 years and diagnosed with severe CHE of at least6 months' duration and refractory to standard therapy.Severity was defined according to the Physician GlobalAssessment (PGA; Table 1). The severity of each PGA sign orsymptom was described in the modified Total Lesion Symp-tom Score (mTLSS; Table 2). Together, the PGA and mTLSSwere developed as a verbal description corresponding to CHEseverity grades depicted in a recently published and validatedphotographic guide.9This photographic guide was distributedto each study investigator as an aid to evaluating CHE severity.Refractory status was verified by the following four criteria.(i) Patients had received treatment with topical corticosteroidsfor at least 8 weeks, within 6 months before enrolment, witheither no response or only a transient response. This previous8 weeks' treatment included 4 weeks of therapy with the mostpotent class of topical corticosteroids (e.g. clobetasol propio-nate). (ii) Patients had also received standard skin care,including emollients and barrier protection as appropriate,without significant improvement. (iii) Patients had avoidedirritants and allergens, if identified, without significantimprovement. (iv) Other conditions which may mimic CHEhad been excluded.Enrolment was open to patients with all types of CHE.Investigators were required to rule out alternative diagnosesincluding infectious dermatoses, psoriasis and active contactdermatitis. All patients were patch-tested within 6 monthsbefore randomization. Women of childbearing potential wererequired to use at least two forms of contraception for at least1 month before starting treatment, during treatment, and forat least 1 month after finishing treatment; these women werealso required to take monthly pregnancy tests **Excluded criteria:** Investigators were required to rule out alternative diagnosesincluding infectious dermatoses, psoriasis and active contactdermatitis. All patients were patch-tested within 6 monthsbefore randomization. Women of childbearing potential wererequired to use at least two forms of contraception for at least1 month before starting treatment, during treatment, and forat least 1 month after finishing treatment; these women werealso required to take monthly pregnancy tests.Patients were excluded from the study if they had psoriasis,or atopic dermatitis treated with prescription drugs, or activebacterial, fungal or viral infection of the hands, or allergiccontact dermatitis of the hands and were unable to avoidexposure to the allergen, or other skin diseases likely to interfere with the conduct or evaluation of

	the study. Patientswere also excluded if they had alanine aminotransferase and/oraspartate aminotransferase values > 250% of the upper limit ofnormal, triglycerides > 200% of the upper limit of normal,cholesterol or low density lipoprotein (LDL) cholesterol values> 200% of the upper limit of normal, haemoglobin belowthe lower limit of normal, a score of 20 or higher on theCentre for Epidemiological Studies Depression scale (CES-D),or a history of major psychiatric disorders. Other exclusioncriteria were treatment with other investigational drugs withinthe previous 2 months, or UVB phototherapy, psoralen andultraviolet A radiation (PUVA) or X-ray radiation, or systemiccorticosteroids, retinoids, or immunosuppressants within theprevious 4 weeks, or drugs with potential for drug–drug inter-actions (such as systemic azoles, erythromycin or clarithromy-cin, simvastatin, or St John's wort) within the previous2 weeks, concomitant retinoids (oral, or topical to hands) orvitamin supplements containing > 2000 IU vitamin A, knownhypersensitivity to retinoids or to any component of the studydrug formulation, or known immunosuppression. **Pretreatment:** Patients in each group had similar demographic and disease characteristics
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: orally once daily after breakfast ● *Dose*: 30 mg alitretinoin. No dose reductions were allowed, but dose inter-ruptions were permitted in case of adverse effects. ● *Duration*: up to 24 weeks (atientswho responded with a PGA assessment of 'clear' or 'almostclear' after 12 weeks stopped treatment at this time, while allothers continued therapy until week 24) Intervention 2 ● *Description*: orally once daily after breakfast ● *Dose*: 10 mg alitretinoin. No dose reductions were allowed, but dose inter-ruptions were permitted in case of adverse effects. ● *Duration*: up to 24 weeks (atientswho responded with a PGA assessment of 'clear' or 'almostclear' after 12 weeks stopped treatment at this time, while allothers continued therapy until week 24) Placebo ● *Description*: orally once daily after breakfast ● *Dose*: placebo ● *Duration*: up to 24 weeks (atientswho responded with a PGA assessment of 'clear' or 'almostclear' after 12 weeks stopped treatment at this time, while allothers continued therapy until week 24)
Outcomes	*Livskvalitet* ● **Outcome type**: ContinuousOutcome *Hyperkolesterolæmi* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (low thyroxine)* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (high TSH)* ● **Outcome type**: DichotomousOutcome *Hypothyroidisme (TSH low)* ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksem (10 mg)* ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksemet (30 mg)* ● **Outcome type**: DichotomousOutcome *Hovedpine* ● **Outcome type**: DichotomousOutcome *Psykose* ● **Outcome type**: DichotomousOutcome *Sværhedsgrad af eksemet* ● **Outcome type**: DichotomousOutcome ● **Scale**: PGA ● **Range**: 0-4 ● **Direction**: Higher is better ● **Data value**: Endpoint ● **Notes**: Reported as clear/ allmost clear
Identification	**Sponsorship source:** Basilea Pharmaceutic **Country:** Germany **Setting:** Multicenter **Comments:** - **Authors name:** Thomas Ruzicka **Institution:** Department of Dermatology, Ludwig-Maximilians-Universita¨t, Frauenlobstr. 9–11, 80337 Munich, Germany **Email:** thomas.ruzicka@med.uni-muenchen.de **Address:** Department of Dermatology, Ludwig-Maximilians-Universita¨t, Frauenlobstr. 9–11, 80337 Munich, Germany
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Quote: "Eligible patients were randomized to treatment by centre, in blocks of 5 without stratification, by the use of computer-gen- erated randomization codes provided by the study sponsor (Basilea Pharmaceutica)"
Allocation concealment	Low risk	Quote: "double-blind coded drug packaging. Placebo, active drug and packaging were indistinguishable. Investigators allocated consecutively numbered packages of medication to patients in their order of enrolment."

Blinding of participants and personnel	Low risk	Quote: "incorporated into double-blind coded drug packaging. Placebo, active drug and packaging were indistinguishable. Investigators allocated consecutively numbered packages of medication to patients in their order of enrolment."
Blinding of outcome assessors	Low risk	Judgement Comment: Presumably blinded outcome assessors
Incomplete outcome data	Low risk	Judgement Comment: ITT analysis.Dropouts:Alitretinoin 30 mg: 106/409Alitretinoin 10 mg: 99/418Placebo: 68/205
Selective outcome reporting	Low risk	
Other sources of bias	High risk	Judgement Comment: Supported by Basilea Pharmaceutica. 3 authors are employees at BP.

Footnotes

Characteristics of excluded studies

Bissonnette 2010a

Reason for exclusion	Poster presentation

Cambazard 2010

Reason for exclusion	Poster presentation

Diepgen 2010

Reason for exclusion	Poster presentation

Dirschka 2011

Reason for exclusion	Poster presentation

Garnock Jones 2009

Reason for exclusion	Wrong study design

Ingram 2009

Reason for exclusion	Already included

Jungersted 2010

Reason for exclusion	Wrong study design

King 2014

Reason for exclusion	Wrong study design

Lynde 2010

Reason for exclusion	Wrong study design

Lynde 2010a

Reason for exclusion	Wrong study design

Lynde 2012

Reason for exclusion	Wrong study design

Scheinfeld 2007

Reason for exclusion	Wrong study design

Schindler 2014

Reason for exclusion	Wrong study design

Schmith 2015

Reason for exclusion	Wrong study design

Schmitt Hoffmann 2011

Reason for exclusion	Wrong comparator

Scott Lang 2011

Reason for exclusion	Poster presentation

Sculpher 2010

Reason for exclusion	Wrong study design

Tan 2015

Reason for exclusion	Wrong study design

Thyssen 2014

Reason for exclusion	Wrong patient population

Winther 2014

Reason for exclusion	Wrong study design

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Bissonnette 2010

Bissonnette,R.; Worm,M.; Gerlach,B.; Guenther,L.; Cambazard,F.; Ruzicka,T.; Maares,J.; Brown,T. C.. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. The British journal of dermatology 2010;162(2):420-6. [DOI:]

Fowler 2014

Fowler,Joseph F.; Graff,Ole; Hamedani,Abbas G.. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. Journal of drugs in dermatology : JDD 2014;13(10): 1198-204. [DOI:]

Ruzicka 2004

Ruzicka,Thomas; Larsen,Frederik Gronhoj; Galewicz,Dorota; Horvath,Attila; Coenraads,Peter Jan; Thestrup-Pedersen,Kristian; Ortonne,Jean Paul; Zouboulis, Christos C.; Harsch,Martin; Brown,Thomas C.; Zultak,Maurice. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. Archives of Dermatology 2004;140(12):1453-9. [DOI:]

Ruzicka 2008

Ruzicka,T.; Lynde,C. W.; Jemec,G. B. E.; Diepgen,T.; Berth-Jones,J.; Coenraads,P. J.; Kaszuba,A.; Bissonnette,R.; Varjonen,E.; Hollo,P.; Cambazard,F.; Lahfa,M.; Elsner,P.; Nyberg,F.; Svensson,A.; Brown,T. C.; Harsch,M.; Maares,J.. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. The British journal of dermatology 2008;158(4):808-17. [DOI:]

Excluded studies

Bissonnette 2010a

Bissonnette R.; Maares J.; Shear N.. Alitretinoin is well tolerated in the treatment of severe chronic hand eczema. Journal of the American Academy of Dermatology 2010;62(3):AB51. [DOI:]

Cambazard 2010

Cambazard F.; Sebastian M.; Lynde C.; Maares J.; Brown T.; Ruzicka T.. Increased efficacy after prolonged treatment with alitretinoin 30 mg in chronic hand eczema patients who did not respond to initial course of treatment. Contact dermatitis 2010;63(Web Page):67-68. [DOI:]

Diepgen 2010

Diepgen T.L.; Zimmermann T.. Alitretinoin therapy for patients with severe chronic hand eczema: Comparing non-interventional studies against randomized controlled clinical trial. Contact dermatitis 2010;63(Web Page):70-71. [DOI:]

Dirschka 2011

Dirschka,T.; Reich,K.; Bissonnette,R.; Maares,J.; Brown,T.; Diepgen,T. L.. An open-label study assessing the safety and efficacy of alitretinoin in patients with severe chronic hand eczema unresponsive to topical corticosteroids. Clinical and experimental dermatology 2011;36(2):149-54. [DOI:]

Garnock Jones 2009

Garnock-Jones,Karly; Perry,Caroline M.. Alitretinoin: in severe chronic hand eczema. Drugs 2009;69(12):1625-34. [DOI:]

Ingram 2009

Ingram J.R.; Batchelor J.M.; Williams H.C.. Alitretinoin as a potential advance in the management of severe chronic hand eczema. Archives of Dermatology 2009; 145(3):314-315. [DOI:]

Jungersted 2010

Jungersted,Jakob Mutanu; Hogh,Julie K.; Hellgren,Lars I.; Jemec,Gregor B. E.; Agner,Tove. Changes in skin barrier during treatment with systemic alitretinoin: focus on skin susceptibility and stratum corneum ceramides. Archives of Dermatological Research 2010;302(9):653-6. [DOI:]

King 2014

King T.; McKenna J.; Alexandroff A.B.. Alitretinoin for the treatment of severe chronic hand eczema. Patient Preference and Adherence 2014;8(Web Page):1629-1634. [DOI:]

Lynde 2010

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Lynde 2010a

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Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

Data and analyses

1 Alitretinoin vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 10mg	2	781	Risk Ratio (IV, Random, 95% CI)	1.57 [1.19, 2.06]
1.1.2 20mg	1	158	Risk Ratio (IV, Random, 95% CI)	1.49 [0.94, 2.34]
1.1.3 30mg	2	1210	Risk Ratio (IV, Random, 95% CI)	2.78 [2.23, 3.48]

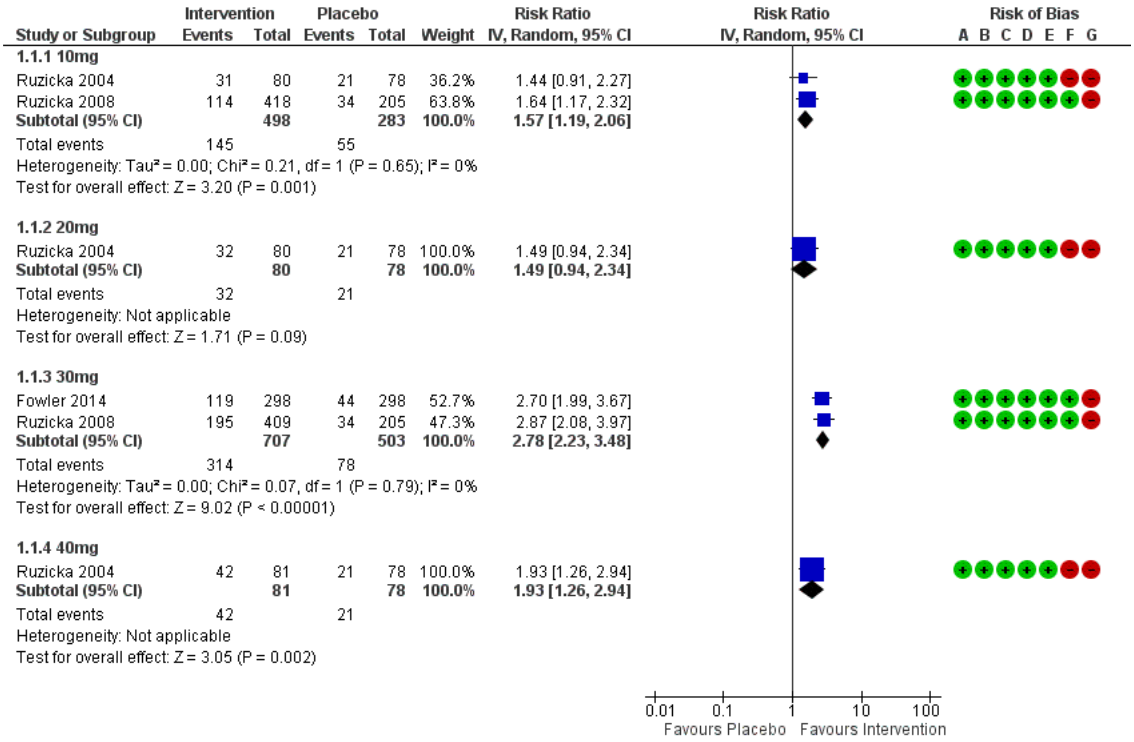
1.1.4 40mg	1	159	Risk Ratio (IV, Random, 95% CI)	1.93 [1.26, 2.94]
1.2 Hovedpine	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 10mg	2	781	Risk Ratio (IV, Random, 95% CI)	1.13 [0.36, 3.58]
1.2.2 20mg	1	158	Risk Ratio (IV, Random, 95% CI)	1.11 [0.42, 2.93]
1.2.3 30mg	2	1210	Risk Ratio (IV, Random, 95% CI)	3.54 [2.51, 4.98]
1.2.4 40mg	1	159	Risk Ratio (IV, Random, 95% CI)	2.89 [1.30, 6.41]
1.3 Hyperkolesterolæmi, Længste follow up	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.3.1 10mg	2	781	Risk Ratio (IV, Random, 95% CI)	1.48 [0.61, 3.59]
1.3.2 20mg	1	158	Risk Ratio (IV, Random, 95% CI)	2.92 [0.99, 8.68]
1.3.3 30mg	1	614	Risk Ratio (IV, Random, 95% CI)	4.76 [2.09, 10.86]
1.3.4 40mg	1	159	Risk Ratio (IV, Random, 95% CI)	4.81 [1.72, 13.45]
1.4 Hypothyroidisme (low thyroxine), Længste follow up	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.4.1 10mg	2	781	Risk Ratio (IV, Random, 95% CI)	0.95 [0.04, 20.30]
1.4.2 20mg	1	158	Risk Ratio (IV, Random, 95% CI)	2.92 [0.61, 14.05]
1.4.3 30mg	1	614	Risk Ratio (IV, Random, 95% CI)	4.52 [0.24, 83.59]
1.4.4 40mg	1	159	Risk Ratio (IV, Random, 95% CI)	3.37 [0.72, 15.73]
1.5 Hyperthyroidisme (high TSH), Længste follow up	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.5.1 10mg	1	623	Risk Ratio (IV, Random, 95% CI)	0.49 [0.12, 1.94]
1.5.2 30mg	1	614	Risk Ratio (IV, Random, 95% CI)	0.50 [0.13, 1.98]
1.5.4 40mg	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.6 Hypothyroidisme (TSH low), Længste follow up	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 10mg	1	623	Risk Ratio (IV, Random, 95% CI)	2.45 [0.85, 7.08]
1.6.2 30mg	1	614	Risk Ratio (IV, Random, 95% CI)	3.51 [1.25, 9.87]
1.6.4 40mg	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.7 Livskvalitet	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8 Psykose	0		Risk Ratio (IV, Fixed, 95% CI)	No totals

2 Alitretinoin vs placebo, by disease category

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 10mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Hyperkeratotic ezcema	2	662	Risk Ratio (IV, Random, 95% CI)	2.05 [1.47, 2.86]
2.1.2 Fingertip eczema	2	330	Risk Ratio (IV, Random, 95% CI)	1.51 [0.99, 2.29]
2.1.3 Pompholyx	2	197	Risk Ratio (IV, Random, 95% CI)	1.30 [0.70, 2.39]
2.2 20mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Hyperkeratotic ezcema	1	136	Risk Ratio (IV, Random, 95% CI)	1.72 [1.02, 2.90]
2.2.2 Fingertip eczema	1	53	Risk Ratio (IV, Random, 95% CI)	1.18 [0.50, 2.77]
2.2.3 Pompholyx	1	38	Risk Ratio (IV, Random, 95% CI)	0.90 [0.26, 3.08]
2.3 40mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.3.1 Hyperkeratotic ezcema	1	131	Risk Ratio (IV, Random, 95% CI)	2.61 [1.61, 4.23]
2.3.3 Fingertip eczema	1	63	Risk Ratio (IV, Random, 95% CI)	2.59 [1.27, 5.28]
2.3.4 Pompholyx	1	41	Risk Ratio (IV, Random, 95% CI)	2.03 [0.70, 5.87]
2.9 30mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.9.1 Hyperkeratotic ezcema	1	519	Risk Ratio (IV, Random, 95% CI)	3.94 [2.60, 5.97]
2.9.2 Fingertip eczema	1	297	Risk Ratio (IV, Random, 95% CI)	2.49 [1.59, 3.89]
2.9.3 Pompholyx	1	166	Risk Ratio (IV, Random, 95% CI)	2.04 [1.06, 3.91]
2.10 30-40mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.10.1 Hyperkeratotic ezcema	2	650	Risk Ratio (IV, Random, 95% CI)	3.27 [2.19, 4.89]
2.10.3 Fingertip eczema	2	360	Risk Ratio (IV, Random, 95% CI)	2.52 [1.73, 3.68]
2.10.4 Pompholyx	2	207	Risk Ratio (IV, Random, 95% CI)	2.03 [1.17, 3.55]

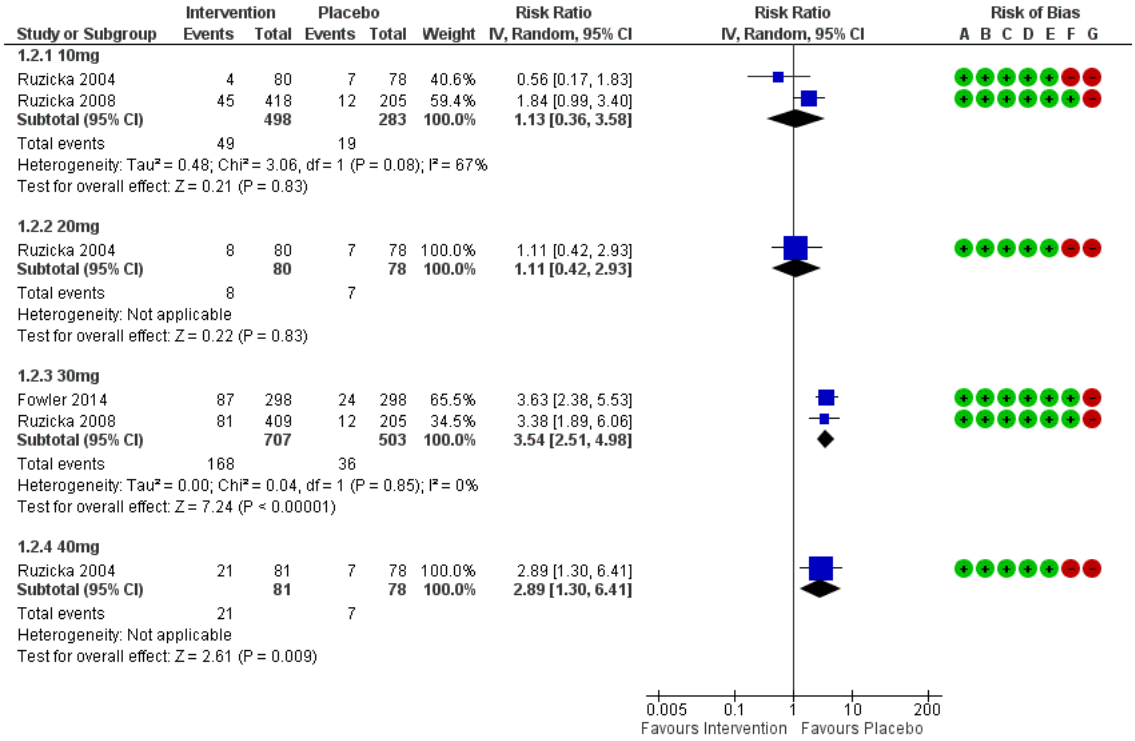
Figures

Figure 1 (Analysis 1.1)



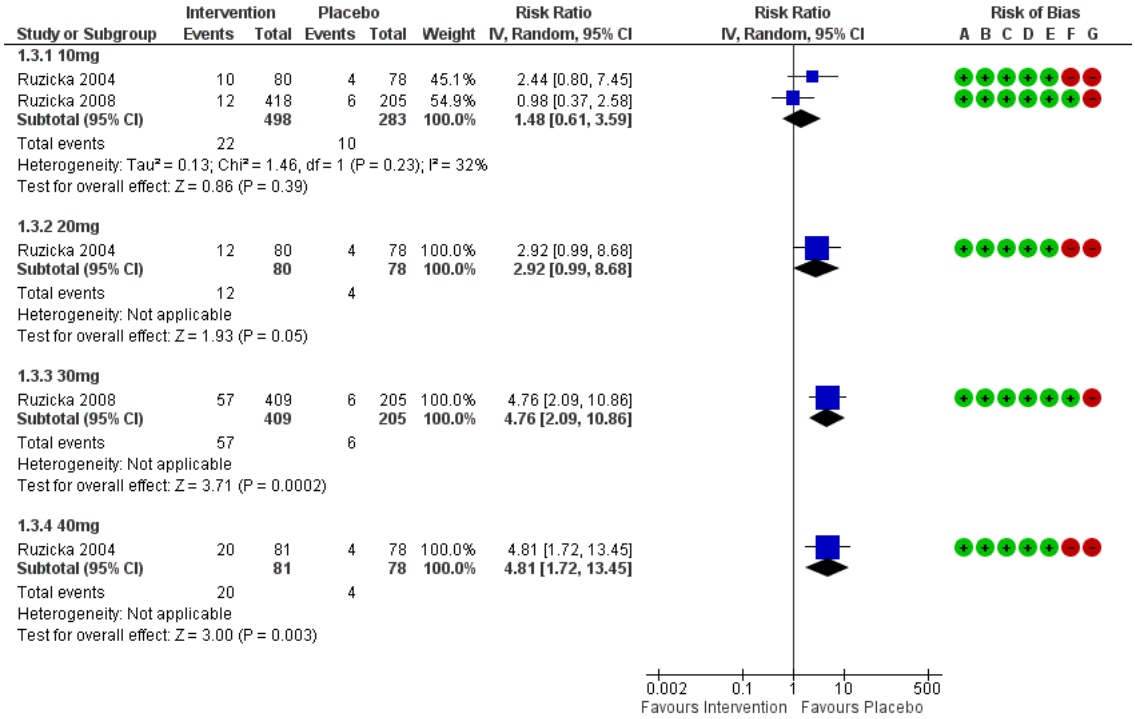
Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.1 Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear).

Figure 2 (Analysis 1.2)



Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.2 Hovedpine.

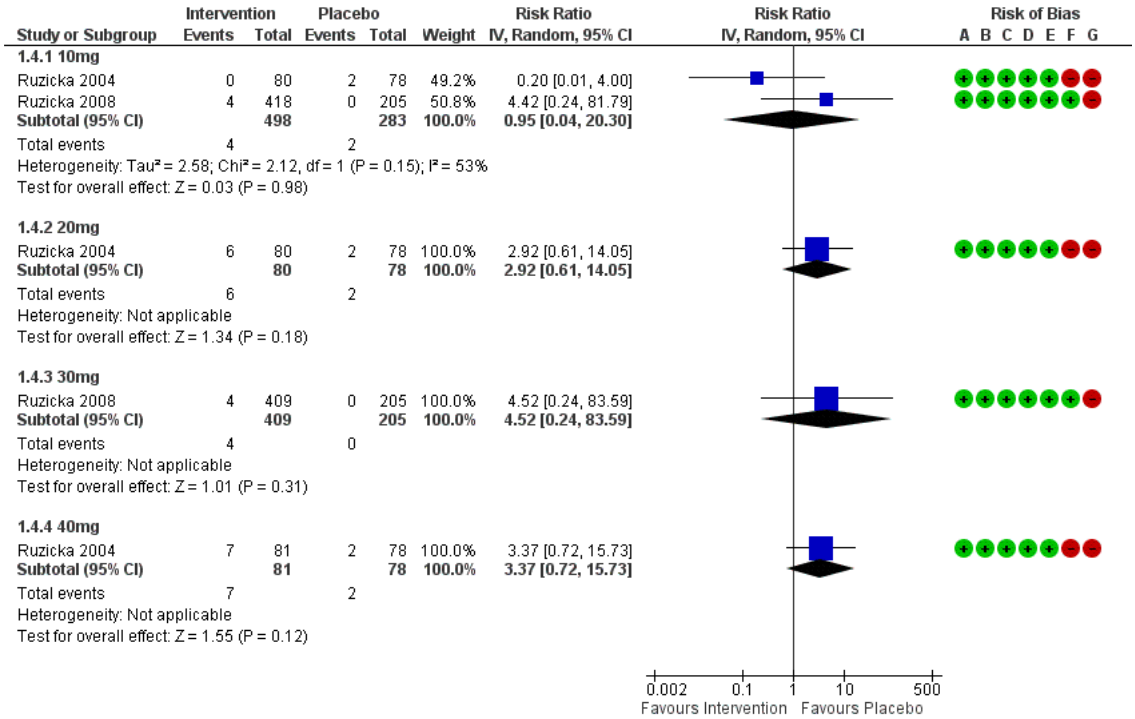
Figure 3 (Analysis 1.3)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.3 Hyperkolesterolæmi, Længste follow up.

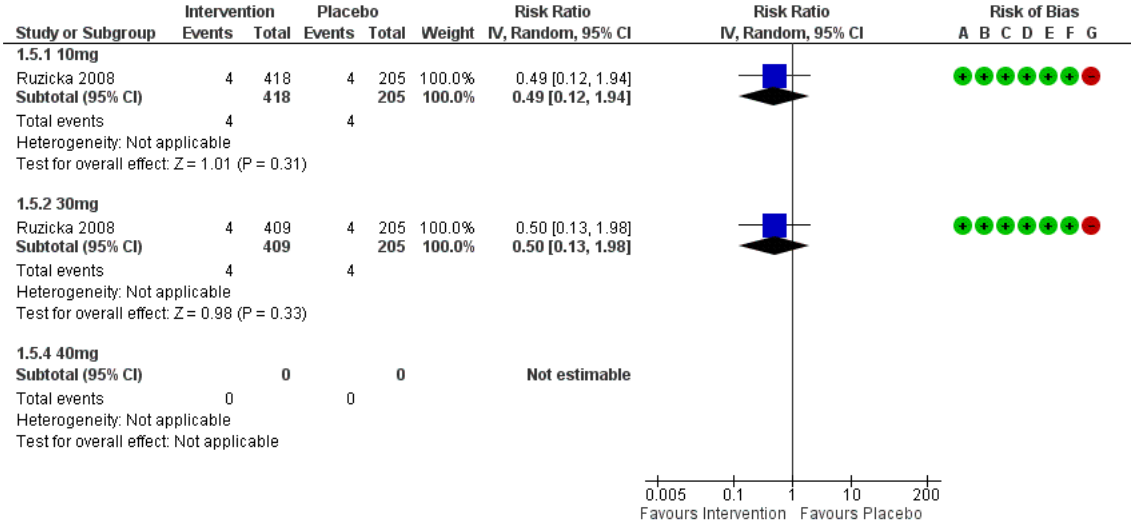
Figure 4 (Analysis 1.4)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.4 Hypothyroidisme (low thyroxine), Længste follow up.

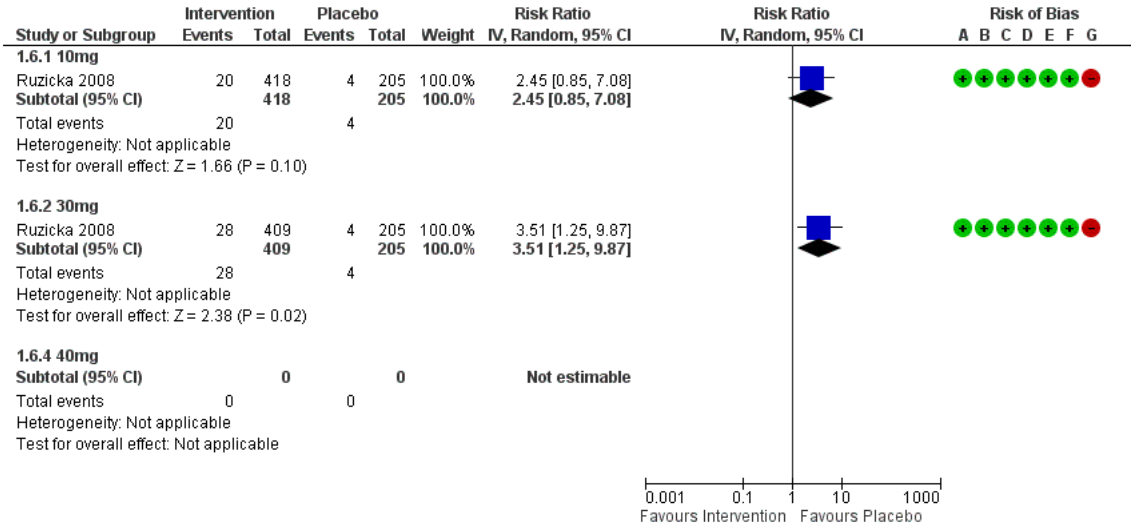
Figure 5 (Analysis 1.5)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.5 Hyperthyroidisme (high TSH), Længste follow up.

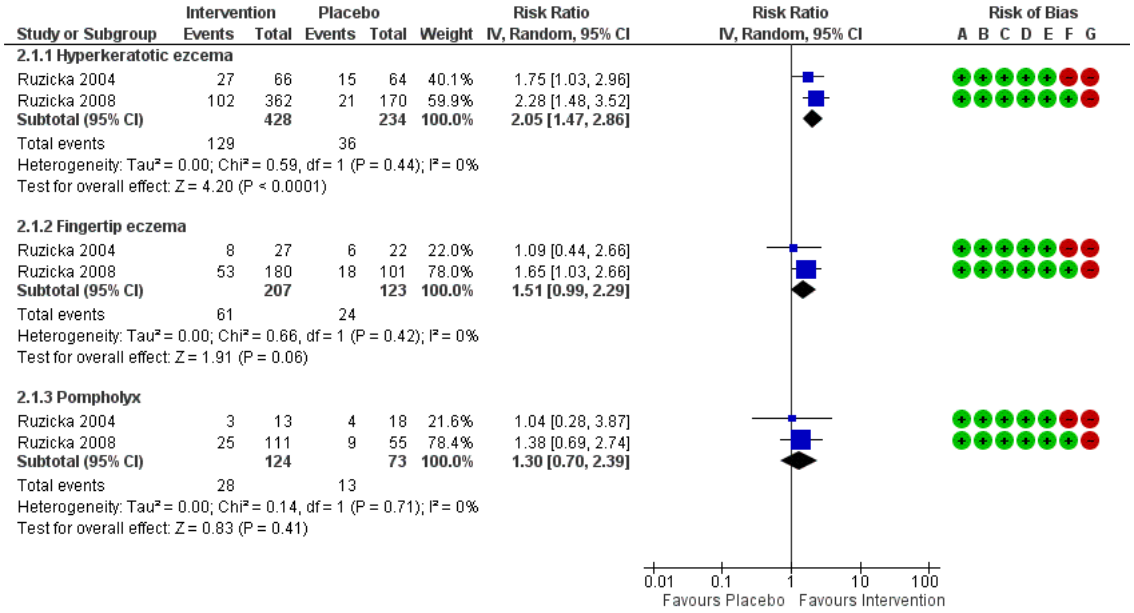
Figure 6 (Analysis 1.6)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

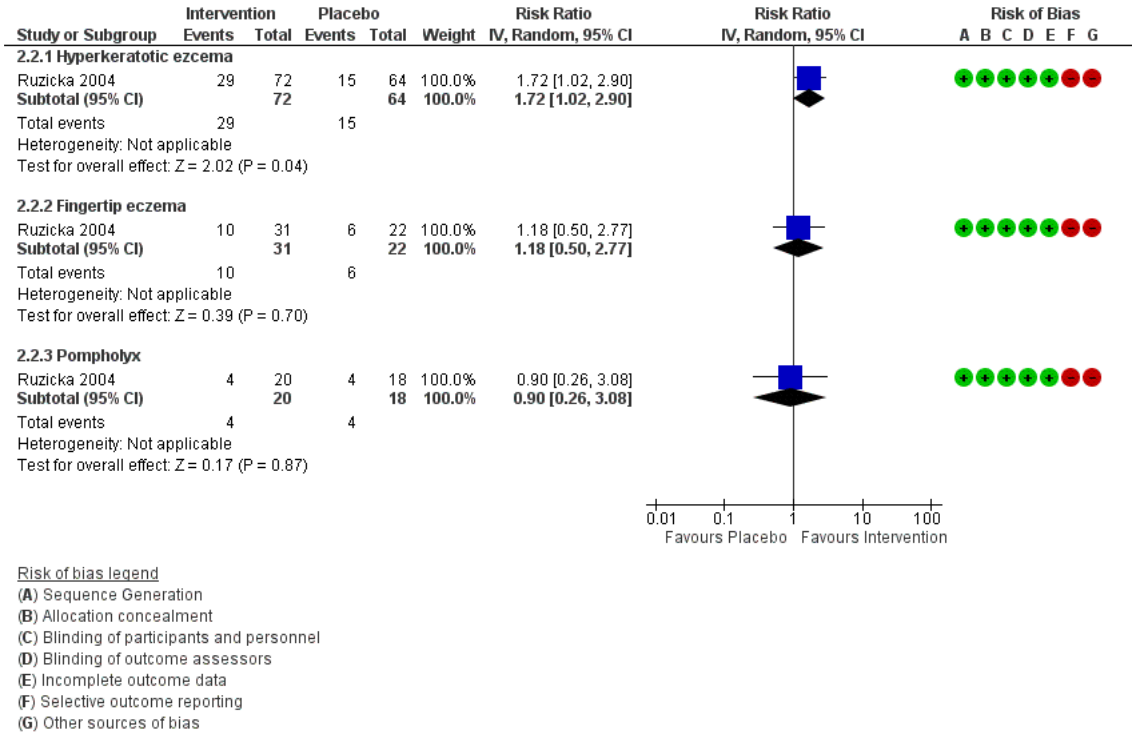
Forest plot of comparison: 1 Alitretinoin vs placebo, outcome: 1.6 Hypothyroidisme (TSH low), Længste follow up.

Figure 7 (Analysis 2.1)



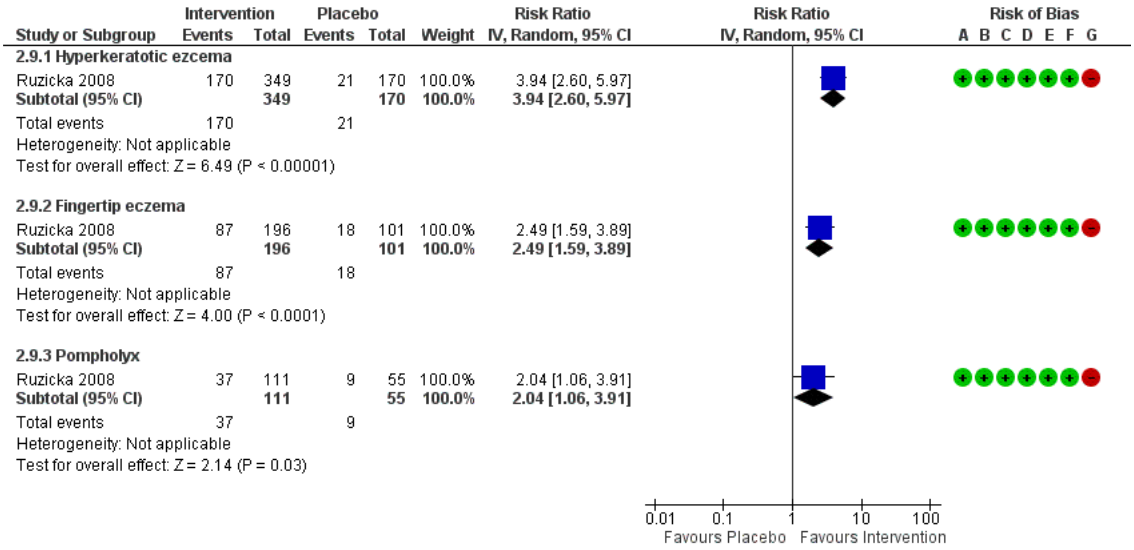
Forest plot of comparison: 2 Alitretinoin vs placebo, by disease category, outcome: 2.1 10mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear).

Figure 8 (Analysis 2.2)



Forest plot of comparison: 2 Alitretinoin vs placebo, by disease category, outcome: 2.2 20mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear).

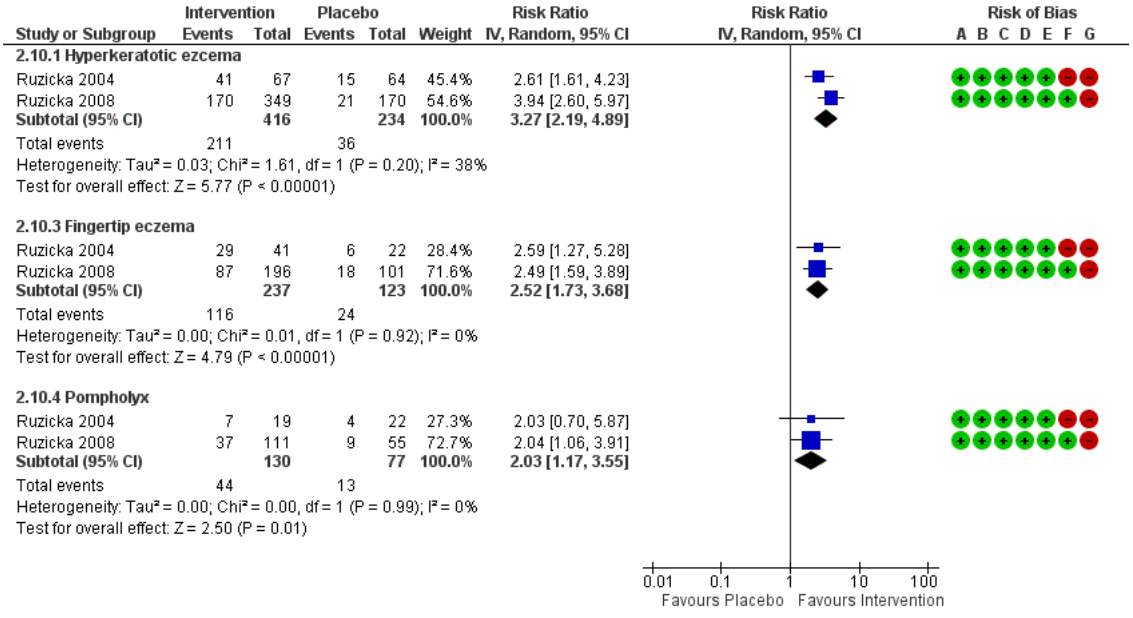
Figure 9 (Analysis 2.9)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 2 Alitretinoin vs placebo, by disease category, outcome: 2.9 30mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear).

Figure 10 (Analysis 2.10)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 2 Alitretinoin vs placebo, by disease category, outcome: 2.10 30-40mg: Sværhedsgrad af eksemet, længste follow up (PGA clear/almost clear).