Drugs of the Future 2007, 32(12): 1040-1045

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.12.1158897

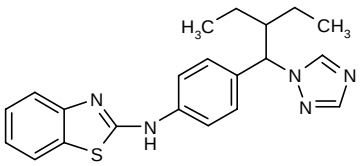
R-115866

Retinoic Acid Metabolism-Blocking Agent
Treatment of Psoriasis
Treatment of Acne

Rambazole™

N-(2-Benzothiazolyl)-*N*-[4-[2-ethyl-1-(1,2,4-triazol-1-yl)butyl]phenyl]amine isomer B

InChI=1/C21H23N5S/c1-3-15(4-2)20(26-14-22-13-23-26)16-9-11-17(12-10-16)24-21
-25-18-7-5-6-8-19(18)27-21/h5-15,20H,3-4H2,1-2H3,(H,24,25)



$C_{21}H_{23}N_5S$
Mol wt: 377.507

CAS: 851811-31-9

CAS: 201410-53-9 (undefined isomer)

CAS: 201410-66-4 ([+]-enantiomer)

CAS: 201410-67-5 ([–]-enantiomer)

EN: 262560

Abstract

R-115866 (Rambazole™) is a second-generation retinoic acid metabolism-blocking agent (RAMBA) developed for the treatment of dermatological disorders such as psoriasis and acne vulgaris. Early studies revealed that R-115866 was highly selective for cytochrome P-450 CYP26A1 (IC_{50} = 4 nM), which is involved in the metabolism of *all-trans*-retinoic acid (ATRA). Orally administered R-115866 proved to be well tolerated in patients with moderate to severe psoriasis or facial acne vulgaris. Clinical studies conducted in patients with moderate to severe psoriasis showed that treatment with R-115866 led to an increase in endogenous ATRA plasma concentrations. In a phase II study, 47% of the patients with moderate to severe psoriasis who received 1 mg oral R-115866 once daily for 8 weeks achieved a 50% or greater reduction in Psoriasis Area Severity Index (PASI) scores. In clinical studies for the treatment of moderate to severe facial acne vulgaris, all lesions, except for closed comedones, were significantly reduced from week 4 onwards. Topical R-115866 also showed encouraging effects in reducing acne lesions.

Synthesis

R-115866 can be obtained as follows. Addition of Gignard reagent (II) to *N*-(4-formylphenyl)acetamide (I) gives the carbinol (III). After conversion of (III) to the mesylate (IV), displacement with 1,2,4-triazole (V) affords the triazolyl derivative (VI). Acid hydrolysis of the acetamido group of (VI) furnishes the aniline (VII). Treatment of aniline (VII) with carbon disulfide and NaOH followed by methylation with iodomethane gives the bis(methylthio)-methylene derivative (VIII). Alternatively, aniline (VII) is converted to the isothiocyanate (IX) by reaction with thiophosgene. The title benzothiazole is finally obtained by condensation of 2-aminobenzenethiol (X) with either (VIII) or (IX) (1). Scheme 1.

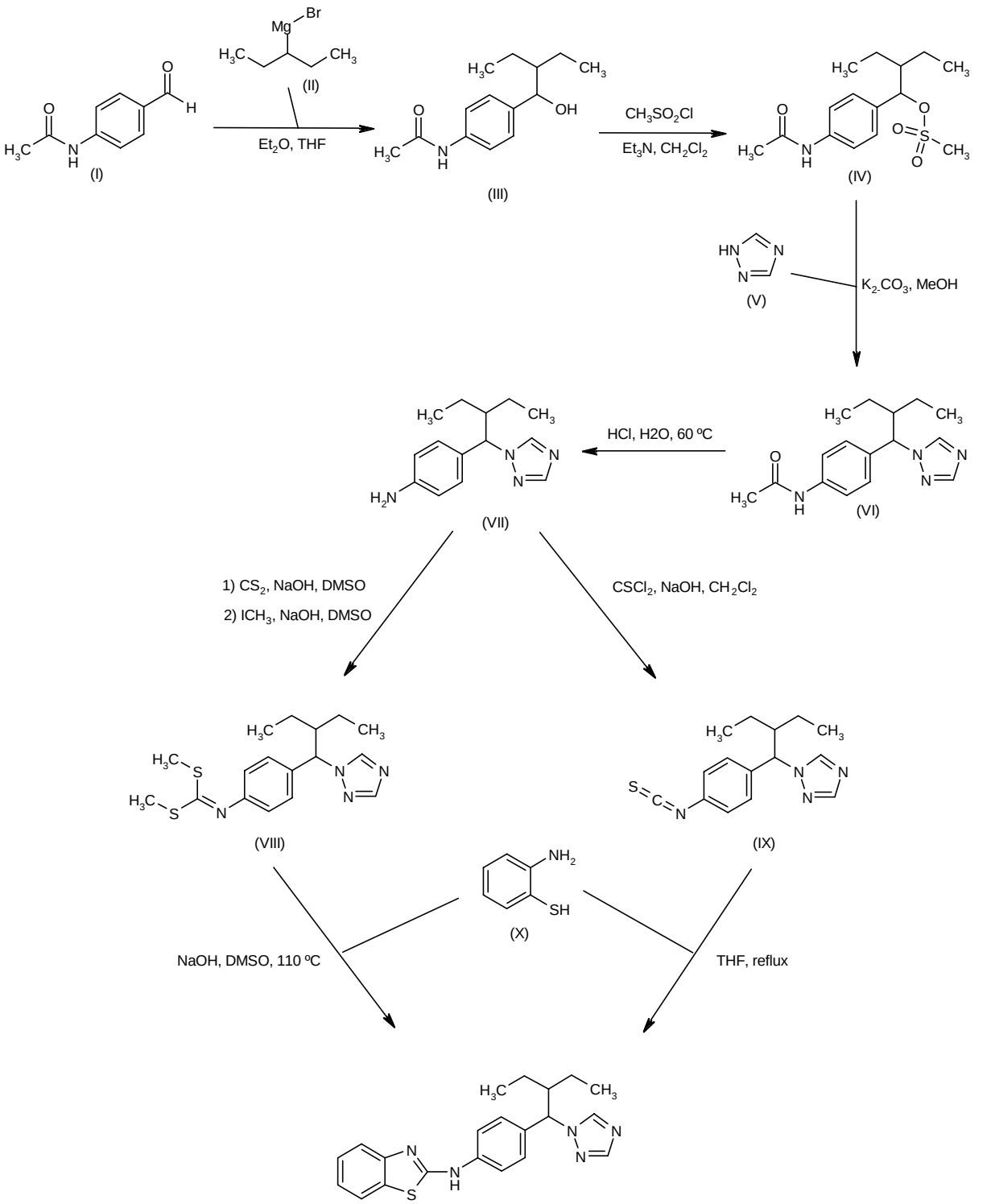
In a different procedure, *N*-(4-bromophenyl)-2-benzothiazolamine (XI) is converted to the lithio derivative and subsequently condensed with 2-ethylbutanal (XII) to give the carbinol (XIII). Treatment of (XIII) with methanesulfonyl chloride and triethylamine provides the mesylate (XIV), which is finally displaced by 1,2,4-triazole (V) yielding the title compound (1). Scheme 2.

Background

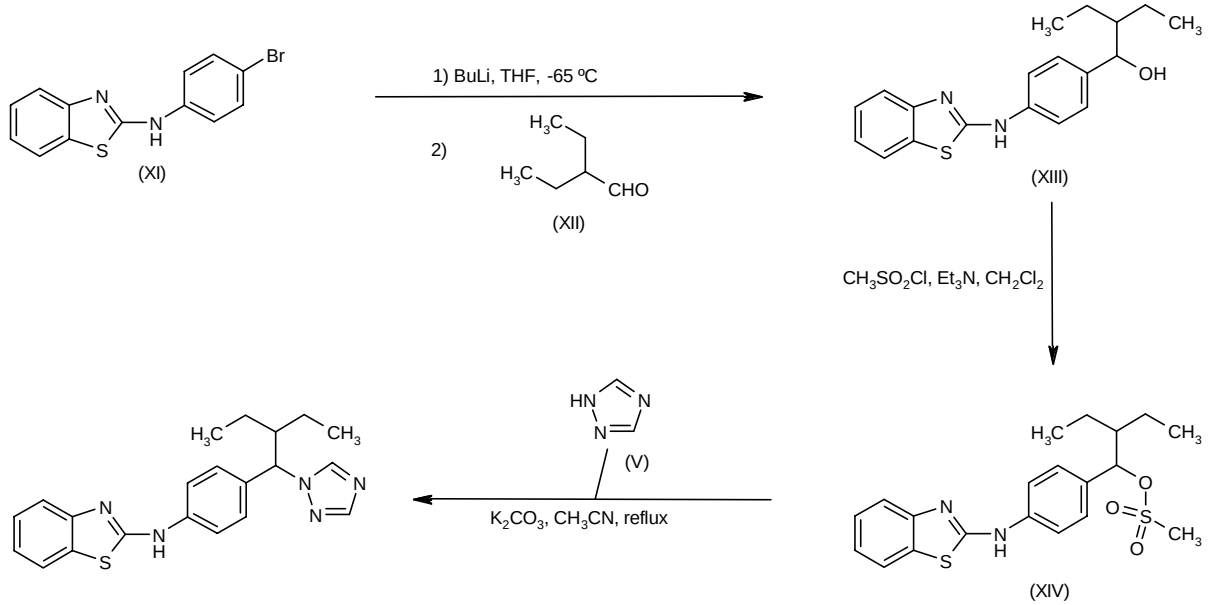
all-trans-Retinoic acid (ATRA), a naturally occurring retinoid, regulates the growth and differentiation of mammalian epithelial tissues via binding to transcription regulatory factors known as retinoic acid receptors (RARs). Unbalanced metabolism of retinoic acid (RA) may lead to retinoid deficiency characterized by hyperkeratinization and desquamation, as seen in dermatological disorders such as acne, psoriasis and ichthyosis. Modulation of RA metabolism therefore represents a promising approach to treat dermatological disorders such as acne and psoriasis. Liarozole, an imidazole derivative, is a first-genera-

Y. Wang. IBC, 8106 Runnymeade Dr., Frederick, MD 21702, USA. N. Serradell. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of R-115866



Scheme 2: Synthesis of R-115866



tion retinoic acid metabolism-blocking agent (RAMBA) proven to inhibit the cytochrome P-450 (CYP)-dependent metabolism of RA and to exert RA mimetic effects. In clinical studies conducted in patients with psoriasis or ichthyosis, liarozole proved to be therapeutically effective. Unfortunately, its lack of CYP isozyme specificity could result in unwanted side effects (2-11).

R-115866 (Rambazole™) is a second-generation RAMBA developed at Barrier Therapeutics. Early studies indicate that R-115866 is a potent inhibitor of human CYP26. The compound is therefore expected to exert therapeutic effects in dermatological conditions such as psoriasis and acne, like liarozole. With its high selectivity for CYP26, which is involved in the metabolism of ATRA, it is expected that R-115866 will have a favorable safety profile (2, 3, 12). R-115866 is currently in phase II clinical development for the treatment of psoriasis (oral) and facial acne (oral and topical).

Preclinical Pharmacology

In vitro studies demonstrated that R-115866 inhibited RA conversion by CYP26A1, a CYP-dependent hydroxylase involved in the catabolism of ATRA, with an IC_{50} of 4 nM compared to 3 μM for liarozole. It was highly selective for this enzyme, as micromolar concentrations were needed for inhibition of other cytochrome P-450 isozymes (CYP19, 17, 2C11, 3A and 2A1). *In vivo*, oral administration to rats at a dose of 2.5 mg/kg induced a marked and transient increase in endogenous RA concentrations in plasma, skin, fat, kidney, spleen and testis, although concentrations in all tissues returned to baseline levels 18 h after administration. R-115866 (0.04-10 mg/kg) also inhibited vaginal keratinization in estrogen-exposed rats in a dose-dependent manner, with an ED_{50} of 1.0 mg/kg (0.6-1.9 mg/kg); at doses of 0.3-2.5 mg/kg, it induced epidermal hyperplasia in mouse ear skin and transformed mouse tail epidermis to an orthokeratotic skin type, and at doses of 0.04-2.5 mg/kg, it upregulated CYP26 mRNA expression in rat liver in a dose-dependent manner. Results from this study also indicated that the keratinization-suppressive and CYP26-inducing activities of R-115866 could be reversed by concomitant administration of AGN-193109, a highly active antagonist of RARs (12, 13).

Topically administered R-115866 also demonstrated retinoid mimetic activity in mice similar to RA. Repeated application to the tail skin produced dose-dependent orthokeratotic transformation, with a significant effect starting at 2 μg (1 μg for RA). R-115866 treatment was not associated with a systemic effect, as indicated by its lack of effect on ear epidermis. The onset of action of R-115866 was faster than RA. Concomitant administration of the RAR antagonist AGN-193109 attenuated the effect on mouse tail epidermis of both R-115866 and RA (14).

In further preclinical studies in mouse, pig, guinea pig and rabbit models, topical R-115866 (0.003-0.1%) also demonstrated potential efficacy in the treatment of psoriasis and acne, as well as photodamage and hyperpigmentation. Results indicated that R-115866 exerts similar

therapeutic effects to RA, but with potentially much milder skin irritation (15).

Pharmacokinetics and Metabolism

The metabolism and excretion of orally administered [^{14}C]-R-115866 (5 mg/kg as a single dose) were studied in mice, rats and dogs. In these species, R-115866 was primarily cleared via metabolism and excreted mainly in the feces. R-143191, a 6-hydroxy-2-benzothiazolamine derivative, was prominent in all species. In all the animals tested, the majority of the radioactivity (82.7% and 91.6%, respectively, for male and female mice, 77.5% and 77.5%, respectively, for male and female rats, and 88.7% and 89.0%, respectively, for male and female dogs) was excreted via the feces (16).

A gas chromatography-high-resolution mass spectrometry method has been developed for the determination of R-115866 in human plasma and validated in healthy volunteers (17).

The pharmacokinetics of oral R-115866 were further evaluated in phase I single- and multiple-dose studies. Healthy male volunteers were administered single doses of 0.6-20 mg p.o. or twice-daily doses of 0.5-4 mg for 8 days, or placebo. The results indicated that it was rapidly absorbed, with peak plasma concentrations detected at approximately 1 h after intake. C_{max} and AUC increased with dose. Steady-state plasma concentrations of R-115866 were achieved after 1 day of multiple dosing, and the terminal half-life of the drug was approximately 15 h (18).

In a phase IIa study in patients with moderate to severe psoriasis treated with R-115866 1 mg p.o. once daily for 8 weeks, the peak plasma concentration of R-115866 was 1.390 ng/ml and the minimum concentration was 0.140 ng/ml, with a t_{max} of 1-2 h. The mean plasma concentrations of the drug remained relatively stable throughout the 8-week treatment period (19).

Safety

The safety and tolerability of single (0.6, 1.25, 2.5, 5, 10 or 20 mg) and multiple oral doses (0.5, 2 and 4 mg or twice a day for 8 days) of R-115866 were first evaluated in a placebo-controlled trial conducted in male volunteers. Administration of R-115866 did not induce clinically relevant changes in laboratory or cardiovascular variables. No serious adverse events (AEs) or deaths were reported and no patients withdrew from the study because of AEs. In the single-dose study, 3 of 6 patients receiving 1.25 mg and 2 of 6 patients receiving 2.5 mg R-115866 experienced AEs, and all subjects receiving 5 mg or above experienced AEs, including erythema and peeling. In the multiple-dose study, doses of 0.5 and 2 mg were well tolerated and were recommended for future clinical studies (18, 20).

R-115866 was well tolerated in the phase IIa study in 19 patients with psoriasis, AEs being generally mild to moderate in intensity. Severe pruritus occurred in 5 patients and severe xerosis in 2 patients. Other severe AEs included cheilitis, increased blood triglycerides, skin fragility, skin pain and atrial fibrillation. Cheilitis was the most frequently recorded AE (n=11) and was considered very likely or probably related to the treatment. Pruritus, xerosis, increased triglycerides and epistaxis were also considered very likely or probably related to treatment. During the study, a total of 16 patients experienced skin or appendage disorders and 13 patients reported gastrointestinal disorders. Three patients withdrew from the study due to AEs, but no deaths or serious AEs were reported (13, 19, 21).

Oral R-115866 was also well tolerated in an exploratory trial in the treatment of acne vulgaris. Sixteen of the 17 treated patients completed the study and 9 experienced a total of 16 AEs, including 10 mild, 5 moderate and 1 severe reaction (eczema); however, all the AEs resolved by the end of the study. Six AEs were considered possibly and 1 AE was considered very likely related to treatment. AEs reported in more than 1 patient were: dry skin (n=3), contact dermatitis (n=2) and eczema (n=2). No deaths or serious AEs were reported. Elevated triglyceride concentrations were reported in 3 patients but this was not considered an AE (22).

Clinical Studies

The efficacy of oral R-115866 was also evaluated in the open-label, multicenter phase IIa trial in 19 patients with moderate to severe plaque-type psoriasis receiving a dose of 1 mg once daily for 8 weeks, followed by a 2-week follow-up period. After 1 week of treatment, the median Psoriasis Area Severity Index (PASI) score was significantly reduced by 7.8% compared to baseline, which increased to 49% at the end of the follow-up period. At the end of the study, 26% of the patients achieved at least a 50% reduction in their baseline PASI scores. At the end of the 2-week follow-up period, further improvement in PASI was observed, with 47% of the patients showing a 50% or greater reduction in PASI scores. Treatment duration was therefore suggested to go beyond 8 weeks to achieve optimal clinical efficacy. According to overall evaluation of efficacy by the investigator, 44% and 64% of patients, respectively, showed at least moderate improvement at the end of treatment and at follow-up. Significant reductions in lesion severity and significant improvements in patient self-assessment were also reported at the end of treatment and at follow-up (13, 19, 21, 23).

As part of this trial, an immunohistochemical study was conducted in 8 patients to assess the dynamics of epidermal proliferation, keratinization, lesional T-cell subsets and cells expressing natural killer (NK) receptors in plaque psoriasis during treatment with R-115866. At week 2, the mean psoriatic plaque severity (SUM) score (6.7 ± 0.4) was almost equal to the baseline value (6.8 ± 0.5). However, at week 8, the plaque severity (4.5 ± 0.8) was reduced from baseline by 34%. Compared with corresponding baseline values, epidermal proliferation, mea-

sured by the mean number of Ki67+ keratinocyte nuclei, was reduced by 63% at week 8, and the expression of K10 was increased by 29%. Interestingly, no induction of retinoid-specific K13 or K19 was observed in the epidermis during the study. Reductions in T-cell subsets and cells expressing NK receptors were observed at week 8, but this was not statistically significant. It should be pointed out that this study was a proof-of-principle trial and the 8-week treatment period was shorter than treatment periods generally needed for retinoids for the treatment of psoriasis. To find the optimal dose and treatment period, further studies are needed (24).

Barrier Therapeutics recently completed a phase IIb dose-finding study of oral R-115866 in patients with moderate to severe psoriasis. The primary objective of this study was to evaluate the dose-ranging response in terms of safety and efficacy of oral R-115866. A total of 176 patients with PASI scores of 10 or above were enrolled in one of four treatment groups. Patients received R-115866 at doses of 0.5, 1 or 2 mg or placebo once daily for 12 weeks. Safety and efficacy assessments were conducted at weeks 2, 4, 8, 12, 16 and 20. According to the Investigator's Global Assessment (IGA), 49% of patients receiving 2.0 mg/day were "cleared or almost cleared" at week 20, whereas only 20% of patients receiving placebo were "cleared or almost cleared" (25).

The efficacy of oral R-115866 (1 mg once daily for 12 weeks) was also examined in the trial in 17 patients with moderate to severe facial acne vulgaris. Efficacy was assessed at baseline, weeks 4, 8 and 12, and at the end of follow-up. At the end of the study (week 12), mean reductions in inflammatory lesions of 77.4%, in noninflammatory lesions of 58.3% and in total lesions of 76.0% were reported. All lesions, except for closed comedones, were significantly reduced from week 4 onwards (22, 26).

In addition to oral R-115866, a topical gel formulation was also tested in a randomized, double-blind, placebo-controlled trial in 15 healthy subjects who applied the gel (0.35% or 0.07%) once daily on intact skin on the buttocks during a 9-day period. Real-time PCR analysis revealed a dose-dependent increase in cellular retinoic acid-binding protein 2 (CRABP-2), the cytokeratin K4 and CYP26A1 expression, and a decrease in K2e and IL-1 expression. In addition, 0.35% R-115866 increased epidermal thickness. One subject experienced mild itching after 8 days of treatment with 0.35% R-115866 gel, but no stinging, burning or vesiculation was reported during the study (27).

Source

Barrier Therapeutics, Inc. (US).

References

1. Lacrampe, J.F.A., Sanz, G.C., Venet, M.G., Mabire, D.J.-P. (Janssen Pharmaceutica NV). *N-[4-(Heteroarylmethyl)phenyl]-heteroarylamines*. EP 907650, JP 2000503670, US 6124330, US 6486187, US 6833375, US 2003176419, WO 9749704.

2. Voorhees, J.J. *Future perspectives for clinical investigation with RAMBAs*. J Eur Acad Dermatol Venereol [14th Congr Eur Acad Dermatol Venereol (EADV) (Oct 12-16, London) 2005] 2005, 19(Suppl. 2): Abst SAT12.5.

3. Njar, V.C.O., Gediya, L., Purushottamachar, P. et al. *Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases*. Bioorg Med Chem 2006, 14(13): 4323-40.

4. Chambon, P. *A decade of molecular biology of retinoic acid receptors*. FASEB J 1996, 10(9): 940-54.

5. Giguère, V. *Retinoic acid receptors and cellular retinoid binding proteins: Complex interplay in retinoid signaling*. Endocr Rev 1994, 15(1): 61-79.

6. Orfanos, C.E., Zouboulis, C.C., Almond-Roestler, B., Geilen, C.C. *Current use and future potential role of retinoids in dermatology*. Drugs 1997, 53(3): 358-88.

7. Muindi, J.R., Frankel, S.R., Huselton, C., De Grazia, F., Garland, W.A., Young, C.W., Warrell, R.P. Jr. *Clinical pharmacology of oral all-trans-retinoic acid in patients with acute promyelocytic leukemia*. Cancer Res 1992, 52(8): 2138-43.

8. Miller, V.A., Rigas, J.R., Muindi, J.R., Tong, W.P., Venkatraman, E., Kris, M.G., Warrell, R.P. Jr. *Modulation of all-trans-retinoic acid pharmacokinetics by liarozole*. Cancer Chemother Pharmacol 1994, 34(6): 522-6.

9. Dockx, P., Decree, J., Degreef, H. *Inhibition of the metabolism of endogenous retinoic acid as treatment for severe psoriasis: An open study with oral liarozole*. Br J Dermatol 1995, 133(3): 426-32.

10. Lucker, G.P., Heremans, A.M.C., Boegheim, P.J., Van de Kerkhof, P.C., Steijlen, P.M. *Oral treatment of ichthyosis by the cytochrome P450 inhibitor liarozole*. Br J Dermatol 1997, 136(1): 71-5.

11. Van Pelt, J.P., De Jong, E.M., De Bakker, E.S., Van de Kerkhof, P.C. *Effects of systemic treatment with liarozole on cutaneous inflammation, epidermal proliferation and differentiation in extensive plaque psoriasis*. Skin Pharmacol Appl Skin Physiol 1998, 11(2): 70-9.

12. Stoppie, P., Borgers, M., Borghgraef, P. et al. *R115866 inhibits all-trans-retinoic acid metabolism and exerts retinoidal effects in rodents*. J Pharmacol Exp Ther 2000, 293(1): 304-12.

13. Verfaille, C.J., Steijlen, P.M., Van de Kerkhof, P.C.M., Stoppie, P., Van Wauwe, J.P., van Rossem, K. *R115866 (Rambazole): A potential alternative for retinoids in the treatment of psoriasis*. J Eur Acad Dermatol Venereol [2nd Int Congr Psoriasis (June 21-24, Paris) 2007] 2007, 21(Suppl. 1): Abst P 017.

14. Stoppie, P., Van Wauwe, J., Wouters, L., Borgers, M. *Rambazole™, a potent inhibitor of all-trans retinoic acid metabolism, applied topically to mouse tail skin exerts retinoid mimetic activity*. 65th Annu Meet Soc Invest Dermal (April 28-May 1, Providence) 2004, Abst 420.

15. Gendimenico, G., Stoppie, P., Van Wauwe, J. et al. *R115866: A selective retinoic acid metabolism inhibitor acts topically as a retinoidal agent in cutaneous model systems*. 62nd Annu Meet Soc Invest Dermatol (May 9-12, Washington, D.C.) 2001, Abst 952.

16. Gu, Z.-M., Wu, D., Feng, H., Barrett, D. *Mass balance, metabolism, and excretion of Rambazole, a novel retinoic acid metabolism-blocking agent (RAMBA) in mice rats and dogs*. 14th

North Am Meet Int Soc Study Xenobiot (ISSX) (Oct 22-26, Rio Grande) 2006, Abst.

17. Verhaeghe, T., Diels, L. *Determination of the retinoic acid metabolism blocking agent R115866 in human plasma by gas chromatography-high resolution mass spectrometry*. Chromatographia 2000, 52(Suppl. S): S-109-12.

18. Cools, M., Gauwenbergh, G., Vanhoutte, F., Vandeplassche, L. *Tolerability, safety and pharmacokinetics of single and multiple oral dosages of R115866 (Rambazole™) in healthy volunteers*. 15th Congr Eur Acad Dermatol Venereol (EADV) (Oct 4-8, Rhodes) 2006, Abst PO35.22.

19. Verfaille, C., Thissen, C.A.C.B., Bovenschen, H.J., Mertens, J., Steijlen, P.M., Van de Kerkhof, P.C.M. *Oral R15866 in the treatment of moderate to severe plaque-type psoriasis*. J Eur Acad Dermatol Venereol 2007, 21(8): 1038-46.

20. Cools, M., Cauwenbergh, G., Vanhoutte, F., Vandeplassche, L. *Tolerability, safety, and pharmacokinetics of single and multiple oral dosages of R115866 in healthy volunteers*. J Am Acad Dermatol [65th Annu Meet Am Acad Dermatol (AAD) (Feb 2-7, Washington, D.C.) 2007] 2007, 56(2, Suppl. 2): Abst P2782.

21. van de Kerkhof, P., Mertens, J., Steijlen, P. *Oral R115866 in patients with moderate to severe plaque-type psoriasis, safety evaluation from a phase IIa trial*. 64th Annu Meet Am Acad Dermatol (AAD) (March 3-7, San Francisco) 2006, Abst P2828.

22. Verfaille, C.J., Coel, M., Boersma, IH., Mertens, J., Borgers, M., Rosseuw, D. *Oral R115866 in the treatment of moderate to severe facial acne vulgaris: An exploratory study*. Br J Dermatol 2007, 157(1): 122-6.

23. Steijlen, P., Thissen, C., Bovenschen, H.J., Mertens, J., van de Kerkhof, P. *Oral Rambazole™, in patients with moderate to severe plaque type psoriasis - A pilot trial*. J Eur Acad Dermatol Venereol [14th Congr Eur Acad Dermatol Venereol (EADV) (Oct 12-16, London) 2005] 2005, 19(Suppl. 2): Abst P06.84.

24. Bovenschen, H.J., Otero, M.E., Langewouters, A.M.G. et al. *Oral retinoic acid metabolism blocking agent Rambazole™ for plaque psoriasis: An immunohistochemical study*. Br J Dermatol 2006, 156(2): 263-70.

25. *Positive phase II data for dose-finding study of oral Rambazole*. DailyDrugNews.com, July 16, 2007.

26. Hachem, J.P., Verfaille, C., Coel, M., Boersma, Mertens, J., Roseeuw, D. *Oral Rambazole™ in the treatment of facial acne vulgaris - A phase IIa trial*. 15th Congr Eur Acad Dermatol Venereol (EADV) (Oct 4-8, Rhodes) 2006, Abst PO165.

27. Cools, M., Pavez-Lorie, E., Borgers, M. et al. *Effect of topical R115866 (Rambazole™) gel on the expression of biomarkers in the skin of healthy volunteers*. 67th Annu Meet Soc Invest Dermatol (May 3-6, Philadelphia) 2006, Abst 240.