Appendix B
Data Compendium

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UV Laser (Monochromatic) Light Therapy for Mild to Moderate Localized Recalcitrant Plaque Psoriasis

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STRATA Skin Sciences supports the need for evidence based decision-making as a fundamental requirement for improving patient outcomes. We hope this compendium assists you in streamlining the data acquisition and review process necessary to ensure the provision of quality, cost-efficient healthcare for your population.

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SECTION 1: PRODUCT INFORMATION

I. INTRODUCTION

a. Psoriasis

Psoriasis is an immune-mediated, genetic disease manifesting in the skin and/or joints. Psoriasis is a serious disease that affects more than 7.5 million people in the United States. Because psoriasis is chronic and unpredictable it can be challenging to treat. Treatment of psoriasis commonly follows a step approach with topical therapy as first line, phototherapy as second line, and systemic medications reserved for when all other treatments fail.

About 80% of people with psoriasis develop plaque psoriasis, the most common form of this disease. Plaque psoriasis is a genetic disease, with a family association in 1 out of every 3 cases. It can develop at any time and, for most people, it appears between the ages of 15 and 35 years. Plaque psoriasis, characterized by well-defined patches of red, raised skin, is most commonly located on the knees, elbows, scalp, trunk, and nails. The severity of psoriasis is measured in terms of its physical and emotional impact. If less than 2% of the body is involved, the case is considered mild. Between 3% and 10% is considered moderate, and more than 10% is severe. Psoriasis is also measured by its impact on quality of life. When psoriasis impairs function (either by involving hands and feet or damaging emotional well-being), the case may be considered severe.

The 308 nanometer (nm) excimer laser has emerged as an important treatment option for patients with stable, localized mild-to-moderate plaque psoriasis, especially for patients whose plaques are recalcitrant to topical therapy. The excimer laser offers numerous benefits to the patient, the physician, and the third-party payor, including:

- At 308 nanometers, the excimer laser utilizes an ultra-narrow wavelength in the narrowband UVB spectrum with a proven anti-psoriatic action. In addition, by focusing the energy exclusively to the psoriasis plaques, the laser avoids potentially detrimental exposure of normal skin to UVB energy.

- UVB and UVA is locally immunosuppressive by its direct effects on Langerhans cells and indirect effects on numerous cytokines and adhesion molecules, which can lead to a switch from a T-helper (Th) 1 to a Th 2 Phenotype. Additional effects include inhibition of both epidermal hyperproliferation and angiogenesis, a selective reduction of in T-lymphocytes within psoriatic skin via apoptotis[80].

- Most patients (84%) will obtain significant improvement (>75%) with 6 to 10 treatments (2 treatments per week for 3 to 5 weeks). These results have proven to be long-lasting as well, with mean remission rates reported from 3.5 to 6 months.

- The excimer laser also has an established cost-effectiveness profile. An economic analysis has demonstrated that the addition of excimer laser treatment results in no expected cost increase to the payor. Additionally, the annual cost of excimer laser treatment is comparable to or less than other standard “Step 2” psoriasis treatment modalities, such as phototherapy treatment alternatives or alternative topical therapies. In addition, the cost-effectiveness of the excimer laser is superior due to the increased number of expected remission days over other forms of therapy.

- It is estimated that there are approximately 7.5 million people in the United States living with psoriasis and approximately 150,000 new cases of psoriasis are diagnosed in the United States each year[97].

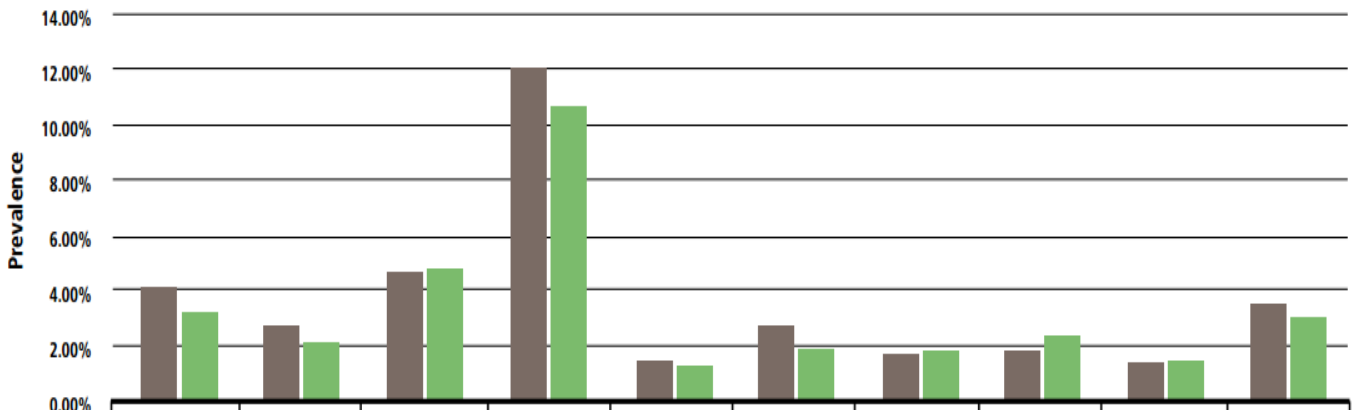
- The value of this procedure has been established by the American Medical Association through the establishment of three specific CPT codes describing this procedure (96920, 96921, 96922), as well as the establishment of Relative Value Units adopted by CMS.

- Numerous private payors and CMS carriers have recognized the clinical and economic merits of this treatment and have adopted medical coverage policies endorsing its use.

The impact of psoriasis on global society is acknowledged in the World Health Organization global report on psoriasis as published in 2016. This report acknowledges the need to not only treat the disease that presents on the skin, but also to treat the cardiovascular and metabolic diseases and psychological conditions that can accompany psoriasis.[98] The report recognizes the socioeconomic burden of the disease and the "apparent upward trend observed in several countries" and requests a call to action for governments and policy-makers to address the following:

1. People suffering from psoriasis to have access to professional medical care
2. Patients suffering from psoriasis to have access to comprehensive, individually adapted treatment
3. Health services shift to a model of people-centered and integrated health services
4. Governments and nongovernmental organizations to provide education on common chronic skin conditions to health-care professionals…to raise awareness and knowledge among general practitioners and to suppport psoriasis research
5. Governments have a key role in reducing stigma and discrimination through campaigns to raise awareness and condemn discrimination of patients who suffer from it

Figure 1. Depicts the prevalence of psoriasis by sex[98]



	Denmark 1978	Germany 2005	Norway 1979–1980	Norway 2007–2008	Spain 1998	Spain 2013	United Kingdom 2009	United States 2001	United States 2003–2004	United States 2009–2010
Male	4.18%	2.71%	4.79%	12.10%	1.46%	2.70%	1.80%	1.90%	1.55%	3.60%
Female	3.29%	2.31%	4.85%	10.80%	1.40%	1.90%	1.90%	2.50%	1.62%	3.10%

The excimer laser treatment for psoriasis is covered by virtually all payers in the United States.

b. Vitiligo and Leukoderma

Vitiligo is a disease that causes the loss of skin color in blotches because the cells that make pigment in the skin (melanin) are destroyed or stop functioning. The cause of this lack of melanocyte function is due to a number of agitators that impair the immune system to the point of autoimmunity, i.e. self-destruction of its own cells and tissues. The extent and rate of color loss from vitiligo is unpredictable and may affect any part of the body; however, it is common for these patches to occur in areas where the skin is exposed to the sun. Vitiligo effects approximately 0.5% - 1% of the world's population and many develop the disease in their twenties. Numerous medications exist for vitiligo including:

- Creams that control inflammation such as a topical corticosteroid
- Vitamin D such as topical calcipotriend (Dononex)
- Medications that effect the immune system, e.g. topicals that contain tacrolimus or pimecrolimus (calcineurine inhibitors)
- Combination medication and light therapy such as psoralen with UVA light (PUV
- Light Therapy – narrow band UVB light
- Laser Therapy – 308nm UVB light via an excimer laser

Leukoderma (leukoderma) is de-pigmentation of the skin marked by the localization or destruction of melanocytes. It is similar to vitiligo clinically, presenting as white patches on the skin. Whereas vitiligo is cause by autoimmunity, leukoderma is typically caused by external factors such as a burn, a cut, or a chemical reaction that destroys the melanocytes resulting in partial or complete loss of color in the specified area. It can affect all ages but typically appears between the ages of 10 years and 30 years.

- The 308 nm excimer laser has proven effective for the purpose of repigmentation. Clinical studies show durable results for repigmentation.
- The excimer laser has an established cost-effectiveness profile for this patient population. Because the results are durable, the cost of treatment is competitive to topicals and biologics.
- Most patients will see significant improvement within 10 treatments, 3x/week; however 20-30 treatments may be needed.

The excimer laser treatment for vitiligo is covered by approximately 50% of payers in the United States.

c. Atopic Dermatitis

Atopic dermatitis is a type of chronic eczematous skin disease; the disease may be inherited and genetically determined. Dry, scaly patches develop in a characteristic distribution and this disease is most common in children and babies during their first year of life. Medications and treatments for atopic dermatitis include:

- Skin creams or ointments that control swelling and lower allergic reactions
- Corticosteroids
- Antibiotics to treat infections caused by bacteria
- Antihistamines that make people sleepy to help stop nighttime scratching
- Drugs that suppress the immune system

- Light therapy (NBUVB)
- A mix of light therapy and a drug called psoralen (PUVA)
- Skin care that helps heal the skin and keep it healthy
- Protection from allergens

The excimer laser has been proven safe and effective for treatment of chronic cases of moderate to severe atopic dermatitis.

- Atopic dermatitis is one of the most common skin diseases, with an estimated prevalence in the United States of 9%. Studies report the incidence is increasing annually.
- Eighty percent of children show good to excellent results following treatment
- Studies show reduced itching by 81% in four weeks

The excimer laser treatment for atopic dermatitis is covered by approximately 70% of payors in the United States.

II. GOAL OF THERAPY

The National Psoriasis Foundation (NPF) states the goal of therapy is to find a treatment that achieves the best results with the fewest side effects. Treatment of psoriasis commonly follows a step approach with topical therapy as first line, phototherapy as second line, and systemic medications reserved for when all other treatments fail.

III. PRODUCT DESCRIPTION

The 308nm UV laser energy is a refined source of narrowband ultraviolet light that is limited to one preferred wavelength within the narrowband UVB range. Targeted delivery of the light solely to the psoriatic plaque is enabled with a focused handpiece. Since the energy is targeted only to plaque areas, normal skin areas are unexposed and unaffected; thus, higher light energy can be delivered to the target plaque, which enhances the antipsoriatic action of the light energy delivered. This refined delivery of traditional narrowband UVB light energy as targeted 308nm-only light is a safe and effective treatment for psoriasis.

The ideal treatment candidate for 308nm UV laser light therapy would be a patient with mild or moderate plaque psoriasis, covering less than 20% of body surface area, for whom first-line therapy, such as topical, has been unsuccessful.

IV. TECHNOLOGY EVALUATION

To evaluate whether the use of the 308nm UV (xenon chloride excimer) monochromatic (laser) light therapy improves health outcomes for patients with mild-to-moderate stable, localized plaque-type psoriasis who have failed standard topical therapy, objective evaluation criteria consistent with evidence-based medicine is used. Many standard criteria have been developed for this purpose. Herein, the use of 308nm laser therapy for

psoriasis is evaluated utilizing a set of technology evaluation criteria similar to those employed by many insurers, including:

1. *The technology must have final approval from the appropriate governmental regulatory bodies.*
2. *Scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.*
3. *The technology must improve the net health outcome.*
4. *The technology must be as beneficial as any established alternatives.*
5. *Improvement must be attainable outside the investigational settings.*

Technology Evaluation Details

1. Approval from the appropriate governmental regulatory bodies

The 308nm xenon chloride (XeCl) excimer laser ("XTRAC") obtained 510(k) regulatory Class II clearance by the US Food and Drug Administration in March 2001 via 510(k) number K003705. The intended use was UVB phototherapy for psoriasis and vitiligo. It was the first FDA market-cleared excimer laser system for the treatment of psoriasis.

In August 2003, the indications for use were expanded to include, in addition to psoriasis and vitiligo, atopic dermatitis and leukoderma via Special 510(k): Device Modification" number K031451. The XTRAC Excimer Laser System, model AL7000 is supported by 510(k) numbers K992914, K003705, K011382 and K020847.

Technology improvements were made since the 2001and the previously cleared XTRAC AL 7000, and the XTRAC XL2 ("Ultra") Model AL8000 was FDA cleared in October 2004 via 510(k) number K041943. The intended use is UVB Phototherapy for psoriasis, vitiligo, atopic dermatitis and leukoderma.

The most recent improvements to the technology created a faster and more powerful laser, allowing treatments to be performed up to three times faster than the previous system. It was approved via 510(k) number K073659. The improved technology, known as the XTRAC Ultra2 Excimer Laser System, Model AL10000, and was FDA cleared in March 2008. The intended use is Targeted UVB phototherapy for treatment of the skin conditions including psoriasis, vitiligo, atopic dermatitis and leukoderma.

All lasers are identical in that they are all excimer lasers used to produce monochromatic (308nm) UVB light for the purpose of targeted, dose controlled UVB (dermatological) phototherapy. The difference between the XTRAC Ultra2 Excimer Laser System, Model AL10000 and the identified predicates is an increase in the laser repetition rate, thus allowing quicker patient treatments.

XTRAC received FDA Clearance for the Multi Micro Dose Tip Accessory in August 2018 via 510(k) number K181480. The Multi-Micro Dose (MMD) Tip accessory is indicated for use in conjunction with the XTRAC laser system to filter the NB-UVB light at delivery in order to calculate and individualize the maximum non-blistering dose for a particular patient. The Multi-Micro Dose ("MMD") tip provides another method, separate of the MED mode, for determining the Optimal Therapeutic Dose ("OTD") for each patient. The OTD is the power setting on the XTRAC Phototherapy system customized for each patient that enables the user to provide patient specific treatment doses. As an alternative to the trial and error method of the MED mode, using the MMD Tip can often determine the optimal XTRAC power setting with a single test application.

2. Effect of the technology on health outcomes

a. Clinical efficacy

There is significant scientific evidence to permit conclusions concerning the effect of the technology on health outcomes. The effect of UV light is well documented.

As early as 1923, Dr. Harry Alderson of Stanford University Medical School reported on the positive effects of ultraviolet light to successfully treat psoriasis[1].

In 1981, Parrish et al[2] reported that the most effective ultraviolet light wavelengths for phototherapy for psoriasis are in the range of 300-313nm.

In 1999, Ozawa et al[4] reported that narrow-band (312nm) Ultraviolet B light (narrow-band UVB) was more effective than broad-band UVB (290-320nm) at depleting T-cells from the epidermis and dermis of psoriatic lesions. Psoriasis vulgaris is mediated by activated T-lymphocytes[3] and that the mechanism of action of UVB light is the cytotoxic effect on the infiltrating T-cells, where the mechanism of cell death is apoptosis.

Bonis et al[5] was the first to report the efficacy of the XeCl 308nm excimer for psoriasis in 1997, finding that the cumulative dose required for the complete clearance of psoriatic plaques is six times less with the XeCl excimer laser than with narrowband UVB. They referred to the 308nm laser as a 'super narrowband' UVB light source, i.e., a further refinement of the narrowband UVB wavelengths. As the basis of this conclusion, Bonis et al treated 10 patients with 308nm; for 6 of those patients, a comparative trial versus narrowband UVB was conducted. Complete clearance of psoriasis plaque was achieved in a mean of 8 treatments with the 308nm XeCl excimer laser versus a mean of 30 treatments with the narrowband UVB treatment. Bonis and Kemeny10 subsequently reported that of the 10 patients enrolled in the initial study, 8 remained symptom free on their laser-treated areas after 2 years.

In May 2002 Novak et al[6] took the research one step further and compared the ability of the 308 nm XeCl UVB laser to produce T-cell apoptosis in vitro to the narrow-band UVB (NB-UVB) light. In a clinical study of 21 patients, 48 plaques, with chronic plaque-type psoriasis treated with the 308nm XeCl excimer laser, they reported that the XeCl excimer laser was highly effective in all of the treated plaques **(***P*<0.05**)**. Complete clearance was obtained in a mean of 8 or 9 treatments (range due to different data sets varying impulse intensity and impulse frequency). In the study, both lasers produced T-cell apoptosis, but quantitative induction was greater with the XeCl laser. The results suggested that the more effective induction of T-cell apoptosis an be responsible for the greater clinical efficacy of the XeCl laser compared to NB-UVB.

In June 2002, Feldman et al[12] reported on a multicenter (5-site) clinical study of the 308-nm laser treatment for psoriasis. Study results showed that 72% (66 out of 92) of patients obtained at least PASI 75 (75% clearing) in an average of 6.2 treatments. Eighty-four percent of patients (95% confidence interval [CI], 79%-87%) reached improvement of 75% or better in 10 or fewer treatments.

In November 2002, Trehan and Taylor[11] published on a conventional (step dosing) phototherapeutic protocol13. They reported on a controlled, blinded clinical study of 15 subjects. A blinded, independent panel assessed PASI scores, and showed 100% concordance with investigator assessments. Control psoriasis plaques exhibited no change throughout the treatment and follow-up period. All 15 subjects achieved PASI 95 (95%

clearing) in a mean of 10.6 treatments. Improvement in post treatment PASI scores was statistically significant ($P<0.01$). Mean remission time was 3.5 months.

In June 2003, Taneja et al[14] reported on a controlled study of 14 patients, 44 treated psoriasis plaques, whose plaques were resistant to other therapies (optical, light phototherapy, systemic therapy, or a combination). Laser dosimetry was based on plaque thickness (induration). Compared with controls (untreated plaques), treated plaques showed significant improvement **(**P<0.001) with a mean of 10 treatments (range 4-14). Treated plaques achieved a mean 81% improvement in modified PASI score at the mean of 10 treatments. A mean 50% improvement in modified PASI score was observed 6 months after the last treatment, demonstrating prolonged remission times with this therapy.

In July 2003, Fikrle et al[15] published a 28-patient study utilizing the 308-nm excimer laser for plaque stage psoriasis, with patients receiving between 6 and 10 treatments. Results indicated that 72% of patients achieved at least a 67% reduction in Psoriasis Severity Index (PSI), and 90% of patients achieved at least a 50% reduction in PSI.

Also in July 2003, Bianchi et a[l7] reported on a immunohistochemical study of cutaneous T-cells and apoptosis related molecules in psoriasis. In this study, biopsies were taken and analyzed from psoriatic lesions of 10 patients before and after treatment with 308-nm excimer light. Their results indicated that psoriatic skin after 308-nm monochromatic UV light therapy is associated with significant T-cell depletion and alterations of apoptosis-related molecules accompanied by a decreased proliferation index and clinical remission.

In December 2003, Gerber et al[16] reported on a 142-patient prospective study on plaque psoriasis. In this study, 102 patients were treated using a standard protocol based on a multiple of minimal erythema dose (MED) for uninvolved skin. The subsequent 42 patients were treated as per a dosimetry protocol based on plaque thickness, similar to the Taneja study described above. Utilizing the standard protocol, 85% of patients obtained total clearance (>=90% PASI reduction) in a median of 10.8 treatments (65.7% were at least 90% clear after 10 or less treatments). Utilizing the induration protocol, 84% of patients achieved total clearance in a median of 7.1 treatments (P<0.05).

In April 2004 Choi and Park[68] evaluated the clinical efficacy of the 308-nm excimer laser treatment for various body areas, using different initial UV doses. One hundred forty vitiligo patches from 69 patients were assigned to 4 groups; face and neck, trunk, extremities, and acral and joint areas. They were then treated twice a week, using different initial UV doses. The rate of repigmentation continued to increase with the number of treatments up to 20 sessions, and then showed plateaus between 20 to 30 sessions. On the other hand, the lesions in acral and joint areas showed the worst responses throughout the treatment sessions. Our findings extend previous observations that the 308-nm excimer laser is an effective treatment option for patients with vitiligo.

In May 2004, Novak et al[9] reported on the efficacy of four different UV-emitting light sources in the induction of T-cell apoptosis, with and without UV filters, and determined that the 308nm xenon chloride excimer laser proved to be the strongest apoptosis inducer.

In June 2004, Hadi et al studied the effectiveness of the 308-nm excimer laser for the treatment of vitiligo. Overall 55 spots were treated: 29 (52.8%) had 75% pigmentation or greater, and 35 (63.7%) had 50%

pigmentation or greater. The best results were on the face: of the 21 spots treated 15 (71.5%) had 75% pigmentation, and 16 (76.2%) had 50% pigmentation or greater. Other areas (neck, extremities, trunk, and genitals) had moderate response in comparison to the face. The least response was on the hands and feet; of the 5 spots treated only 20% showed 50% pigmentation or more.

In October 2004, Passeron et al[44] evaluated the efficacy of the 308nm laser in the treatment of mycosis fungoides (MF). Five patients with limited patch-stage (n=2) or plaque-stage (n=3) were included in the study. Skin biopsies were performed before treatment and 1 weeks after the last session. Each patient was treated with 50nJ/cm2 less than the MED. The fluencies were then increased by 100mJ/cm2 every 2 sessions. Treatment was administered twice weekly until >90 improvement was achieved. A clinical response was obtained for 4 out of the 5 patients and minimal residual activity was observed in the fifth patient. Clinical healing was obtained in 11 of 21 sessions (average 15 sessions) with a cumulative dose ranging from 2.4 to 16.1 J/cm2 (average dose, 6.5 J/cm2). Post-therapy specimens showed a marked decrease of the inflammatory infiltrate with loss of epidermotropism and Pautrier microabscesses. No clinical recurrence was noted 3 months after the end of the sessions. The study demonstrated efficacy of the 308nm excimer laser in clearing localized plaque and plaque stage MF.

In March 2005, Pahlajani et al[17] reported on a 16-patient study which compared the excimer laser for psoriasis in pediatric and adult populations. The pediatric group (n=4) achieved a 91% reduction in psoriasis severity score in a mean of 12.5 treatments, while the adult group (n=12) achieved a 62% reduction in a mean of 9.7 treatments. The authors concluded that the 308nm excimer laser appears to be a safe and effective treatment for localized psoriasis in children as well as in adults.

In November 2005, Taibjee[27] et al compared the efficacy of the 308nm excimer laser to pulsed dye laser (PDL) for psoriasis. A within-patient controlled prospective clinical trial of treatment of localized plaque psoriasis was performed on 22 adult patients with a mean Psoriasis Area and Severity Index of 7.1. A total of 15 patients completed treatment. The mean improvement in PSI was 4.7 with excimer and 2.7 with PDL. PSI improvement was significantly greater with excimer than PDL ($P = 0.003$) or both control plaques ($P < 0.001$). Clinical response to treatment was significantly greater for excimer than PDL ($P = 0.003$) or both controls ($P < 0.001$). The study concluded that excimer appeared on average more efficacious.

In May 2006 Nistico[28] researched the efficacy of the 308nm excimer laser for the treatment of palmoplantar psoriasis (PP). Fifty-four patients (29 male and 25 female) affected by PP were treated with MEL every 7-14 days. A mean number of 10 sessions was performed with an increase of the dose depending on patient's skin type and response. All 54 patients completed the treatment. After 4 months of treatment we observed a complete remission in 31 patients, a partial remission in 13 patients, and a moderate improvement in 10 patients. The study concluded that the excimer laser is an effective treatment for selected forms of PP.

In June 2006, Rivard et al[29] backed up the previously reported Nistico research, via research at Henry Ford Hospital, Detroit Michigan, for the treatment of psoriasis, vitiligo, palmoplantar psoriasis and hand dermatitis. A total of 34 patients were treated between January 2003 and February 2005. Of the 28 patients with psoriasis, over 80% had greater than 75% improvement after an average of 12 treatments.

In July 2006, Baltás et al[30] reported on the efficacy of the 308nm excimer laser in atopic dermatitis. Fifteen patient with atopic dermatitis (less than 20% body area involvement) were treated with a xenon chloride

excimer laser (XTRAC laser) twice weekly. The severity of the atopic dermatitis was assessed via (i) a clinical score characterizing the intensity of erythema, infiltration, lichenification and excoriation; (ii) the quality of life, determined by means of a questionnaire; and (iii) a visual linear analogue scale, with which the patients scored the severity of their pruritus. After 1 month of laser therapy, the clinical scores were significantly lower than the initial values. Similar decreases were observed for the quality of life and pruritus scores. No serious or unpleasant side-effects were observed, suggesting that the xenon chloride excimer laser is an effective and well-tolerated treatment for localized atopic dermatitis.

Morison et al[18] investigated thirty-five patients with psoriasis of the scalp unresponsive to intense topical therapy with the excimer (308 nm) laser in August 2006. The patients were treated twice weekly. All patients improved. Seventeen/35 (49%) of patients cleared>95% (mean: 21 treatments; range: 6-52) and 16/35 (45%) cleared 50-95%.

Also in August 2006, Goldinger et al[31] reported on the comparison of Narrow-Band UVB (311nm) versus excimer (308nm) in the treatment of psoriasis Vulgaris. A prospective right/left comparative, open single-blinded trail selected psoriasis plaques of 16 patients. After 12 treatments, 15 patients were evaluated. In 2 patients no difference between the two body sides was observed. In 9 patients, the laser-treated lesions showed better results, whereas in 4 patients the side treated with the 311-nm UVB showed more clearing. The mean reduction in PASI score was 5.6 and 4.9, respectively (difference not significant). It was concluded that the 308nm xenon chloride excimer laser is an additional effective therapeutic option for the treatment of psoriasis vulgaris.

In March 2007, Passeron et al[43] evaluated the use of the 308nm excimer laser for treatment of mycosis fungoides. Ten patients with mycosis fungoides were treated with the excimer laser on a total of 29 lesions (25 patch-stage, 3 plaques and 1 nodule). After determination of the minimal erythemal dose, sessions were started twice weekly gradually increasing in accordance with tolerability. Eighty-six percent of patch-stage or plaque lesions had completely cleared up by the end of treatment and 14% had cleared up partially, with a global response rate of 100%. The mean number of sessions was 15 (6 to 46 sessions) corresponding to a mean treatment duration of 2 months. The mean cumulative dose was 5 J/cm2 (1.3 to 16.1 cm2). Follow-up was performed in 19 lesions for a median period of 15 months (8 to 26 months). Persistent complete clearance was observed in 13 of 19 (68%) lesions (12 patch-stage and 1 plaque). Continued partial clearance was noted in 3 lesions (1 patch-stage and 2 plaques) (16%). Two lesions (both patch-stage) (11%) showed relapse 7 months after the end of treatment. The sole nodule in the study showed no response to treatment. Histologically, the lesion showed healing where it had disappeared, except for one case with a few mycosis cells in the epidermis despite a clinical appearance of healing. The study demonstrated efficacy of the laser for mycosis fungoides.

In August 2007, Zakarian et al[32] completed a review of theories on the reasons behind the enhanced efficacy of 308nm laser over traditional UVB phototherapy. A comprehensive review of literature from 1965 to the present reported that “the possible explanations for the superior efficacy of the excimer laser over traditional UVB therapy for psoriasis include: 1) a higher intensity UV light to plaques, which is more effective in clearing psoriasis; 2) penetration into the dermis where it may induce T cell apoptosis, potentially to a greater extent than the wavelength or given energy level predicts; and 3) the difference in the delivery of UVB light may result in cell death and skin immune system suppression more effectively than traditional UVB.”

In December 2007 an additional report on the efficacy and safety of the 308nm laser for the treatment of psoriasis vulgaris was published by He YL et al[33]. In this study 40 subjects with psoriasis vulgaris (26 macular type, and 14 chronic plaque type) were treated by a 308 nm excimer laser. After a total of 15 treatments, (1) the Psoriasis Area and Severity Index score was improved by 90.19+/-10.12% and 77.34+/-17.04% in macular type and chronic plaque type, respectively ($P<0.05$) and (2) the average treatment sessions were 13.7 times. The study concluded the 308nm excimer laser is safe and effective for the treatment of psoriasis vulgaris.

In February 2008, Nistico et al evaluated the efficacy of monochromatic excimer light (308 nm) in the treatment of atopic dermatitis in adults and children. Twelve adults and six children affected by localized lesions of AD were enrolled in this pilot study and treated with a weekly session of MEL. A range of 6-12 sessions was performed with an increasing dosage according to the patient's phototype and response. Follow-up was for 16 wk. All patients completed the protocol. At the end of treatment complete remission was observed in 12/18 patients (66.7%), a partial remission in 3/18 (16.7%) and no remission in 3/18 (16.7%). A mean total dose of 21.89 minimal erythemal dose (MED) was performed. Forty-four percent of patients maintained the results achieved at a 16-week follow-up. Treatment was well tolerated overall. MEL can be considered as a valid and safe therapeutic option for the treatment of localized AD in adults and children.

In October 2008, Han et al[34] reported on the safety and effectiveness of the 308nm laser in the treatment of psoriasis vulgaris and palmoplantar psoriasis. Thirty-five patients with psoriasis vulgaris and 15 patients with palmoplantar psoriasis were recruited for this study. Thirty patients with psoriasis vulgaris completed a total of 16 treatments with 308-nm MEL twice a week, and 15 patients palmoplantar psoriasis completed 25 treatments administered once weekly. Thirty patients with psoriasis vulgaris completed a total of 16 treatments with 308-nm MEL twice a week. Patients with palmoplantar psoriasis (n=15) showed a 52.5% improvement in the mean severity index score after a total of 25 MEL treatments (1 x /week) with only one patient (6.7%) achieving clearance. The MEL therapy was well tolerated with a low incidence of side effects, which included pruritus, erythema and blister formation, concluding the therapy as safe and effective treatment modality for patients with mild-to-moderate psoriasis vulgaris and palmoplantar psoriasis.

In August 2009 Nistico et al[35] reported on a large scale study of 279 patients with common and persistent skin diseases enrolled into an open prospective study. 152 patients with stable and localized plaque psoriasis, 47 with palmoplantar psoriasis, 7 with palmoplantar pustulosis, 32 with vitiligo, 11 with prurigo nodularis, 9 with mycosis fungoides stage Ia, 8 with alopecia, 5 with localized scleroderma, 5 with genital lichen sclerosus, and 3 with granuloma annulare. The 308 nm excimer light was used at a power density of 48 mW/cm(2). An average of 12 sessions (range, 6-18), one session per week, was performed and yielded a total dose range of 4-12.5 J/cm(2). Complete remission was observed in more than 50% of patients with plaque psoriasis and palmoplantar dermatoses, respectively, complete remission in all patients affected by mycosis fungoides, excellent repigmentation in one third of vitiligo patients, hair regrowth in three patients with alopecia areata, an overall improvement in prurigo nodularis, a partial remission in patients affected by localized scleroderma, and a complete remission in most of the patients with genital lichen sclerosus and granuloma annulare. The study confirms the use of monochromatic excimer light as a valid choice for the treatment of psoriasis, vitiligo, and mycosis fungoides.

In November 2009, Wollenschlager et al[36] reported on the efficacy of the 308nm excimer laser in the treatment of 57 patients with localized, mild therapy-resistant atopic dermatitis. Complete remission was achieved in

nearly 85% of the patients and partial remission was achieved in 15% of the patients after 10 treatments. It was determined that excimer UVB treatment expands the therapeutic options in patients with localized and therapy-resistant atopic dermatitis enormously.

Also in November 2009, Niwa et al[38] evaluated the use of the 308 nm excimer laser in Japanese patients with psoriasis. Seven patients (six men and 1 woman) with plaque-type psoriasis were treated with 308-nm excimer light at 7-14-day intervals. The Psoriasis Severity Index (PSI) was calculated for individual plaques in order to assess the effectiveness of the therapy. A 74.9% mean improvement in the PASI was observed after 10 treatment sessions. These results suggested that targeted irradiation with 308-nm excimer light leads to rapid and selective improvement in plaque-type psoriatic lesions without unnecessary radiation exposure to the surrounding unaffected skin.

In January 2010 Gattu et al[37] performed a pilot study to evaluate the efficacy safety and feasibility of excimer laser utilizing a supre-erythemogenic phototherapy strategy (Phototherapy well beyond the MED dose) to treat generalized psoriasis. After 9 months, 13 patients with psoriasis involving > 10% but < 30% body surface area received laser treatment twice weekly for 12 weeks, with 6 months of post-treatment follow-up. The primary endpoint was percentage of patients achieving Psoriasis Area and Severity Index (PASI) 75. Of the 12 patients who completed the treatment phase, 54% achieved PASI 75. During the 6-month follow-up period 83% maintained PASI 50 with no treatment. The study concluded the laser is an effective treatment with a favorable remission rate.

In May 2010 Brenninkmeijer et al[48] investigated the efficacy and safety of the 308nm XeCl laser compared to 0.05% clobetasol propionate (CP) for the purigo form of atopic dermatitis (AD). In a prospective, randomized, within-patient controlled study 13 patients with a purigo form of AD were randomized to receive the excimer laser on one side and topical CP on the other side. Laser treatment was performed twice a week for 10 weeks. A significant improvement of mean PAIS was seen for the laser and CP at week 10 compared with baseline: 9.2 ($P < 0.01$) improvement for the laser treated areas and 8.0 ($P < 0.01$) for the CP treated areas. During follow up the excimer showed more improvement compared with CP and histological evaluation showed marked decrease of epidermal thickness and inflammatory infiltrate at the laser treated sites.

In July 2010 Le Duff et al[42] published a manuscript on the direct comparison of a 308nm excimer lamp and a 308 nm excimer laser for treating vitiligo; this randomized study was designed for nonsegmentatal vitiligo. Lesions were treated twice weekly with the same dose on both sides for a total of 24 sessions. The evaluation was done by two independent physicians blinded to the treatment on direct light and ultraviolet light photos. A total of 20 patients participated (20 completed) and 104 lesions were treated. The treatment results for efficacy of repigmentation of at least 50% ($P=0.006$); however the lamp induced more erythema than the laser. Both methods were safe and effective.

In October 2010, Hadi et al[39] performed a retrospective chart review of a population-based group of 98 patients with various forms of localized stable psoriasis treated with excimer laser. Of these, 41 were male, and 57 were female patients. Ages ranged from 10 to 84 years (mean, 51.4 years). Patients who completed at least 10 sessions were included unless they had achieved >70% improvement in PASI scores before 10 treatments. The initial dose was determined by the MED (minimal erythema dose), and the dose was raised gradually in a stepwise fashion. Significant improvement (≥70%) was achieved by 59 (60.2%) patients; they needed an average cumulative dose of 6.46 J/cm(2), and an average of 17 sessions. Twenty-four (24.5%) patients achieved

good improvement (50% to 70%); the average cumulative dose needed was 5.36 J/cm(2), and the average number of sessions required was 12. Side effects were limited to sunburn-like reaction. It was concluded the 308-nm excimer laser is an effective and safe modality for the treatment of psoriasis, with good results achieved in a relatively short time.

In June 2011, Furuhashi et al[41] published on an open label study that investigated the efficacy of the 308 nm laser for the treatment of palmoplantar pustulosis. Twenty patients were treated once per week for 30 weeks. Patient response was accessed every 10 sessions based on the Palmoplantar Pustulosis Area and Severity Index (PPPASI) score. At baseline, the mean (±SD) PPPASI score was 19.5 (±8.1) and it decreased steadily throughout the treatment period: 13.2 (±6.6) at 10 treatments, 10.9 (±9.6) at 20 treatments and 9.5 (±8.9) at 30 treatments. The PPPASI score was significantly lower after 20 treatments than at baseline ($P < 0.05$) and even lower after 30 treatments ($P < 0.01$).

Also in June 2011 Do et al[62] published on the effects of the 308nm laser on segmental vitiligo. A retrospective chart review was conducted on 80 patients who had received the excimer therapy for >3 months. The mean grade of repigmentation was 2.3 after 20.6 months of mean treatment duration; 23.8% of 80 patients showed grade 4, 20% showed grade 3, and 56.2% showed grade 1-2 repigmentation. However, none of them achieved complete repigmentation with excimer laser. The degree of repigmentation was positively correlated with treatment duration ($r=0.315$, $P=0.004$) and cumulative ultraviolet (UV) dosage ($r=0.366$, $P=0.001$), whereas it was negatively correlated with disease duration ($r=-0.265$, $P=0.017$). This study suggests that SV has a better repigmentation response when excimer laser is used at earlier stages of the disease and long-term use and high cumulative UV energy of the excimer laser elicit better responses.

Al-Mutairi and Al-Haddad[79] evaluated the therapeutic efficacy and safety of a 308-nm excimer laser for the treatment of scalp and palmoplantar psoriasis in 41 adult patients (25 males and 16 females). 26 patients had lesions localized to scalp, and 15 patients had involvement of palm and soles. The mean age was 44.5 years (range 18-73) and mean duration of psoriasis was 15 years. The initial dose was based on multiples of a predetermined minimal erythema dose, twice weekly for a maximum 12 weeks. Twenty-two of the 23 patients with scalp psoriasis showed improvement, while one patient showed no change; none experienced worsening of symptoms. The mean minimal erythema dose (MED) was found to be 383 mJ/cm(2) (range 180-650 mJ/cm(2)). The cumulative dose of irradiation was 1,841 mJ/cm(2) (range 600-2,500). The percentage improvement from baseline in PASI score was 78.57 %. Side effects were seen in 20 patients (86.96 %) mainly in the form of erythema. Four patients developed mild relapse at the end of 6 months after the therapy. In 15 patients with palmoplantar psoriasis, the mean MED was found to be 415 mJ/cm(2) (range 200-950 mJ/cm(2)). The cumulative dose of irradiation was 28.4-115.5 Jcm(2) (mean 59.1 Jcm(2)). The mean number of treatments to achieve clearance (equal to 90 % reduction of PSI score) was 16. Two patients relapsed at the end of 6 months after the therapy. Investigators concluded the 308-nm excimer laser is an effective, safe, easy, and relatively quicker method for the treatment of psoriasis at difficult to treat sites, with good results in a somewhat short time.

In January 2015, Al-Shobaili[74] published data on 134 vitiligo patients who had completed excimer therapy. The Dermatology Life Quality Index (DLQI) was used to assess the effect of excimer laser treatment on patients' quality of life (QoL). A visual analogue scale (VAS) was used to rate patients' overall life satisfaction and disturbance. Excimer laser treatment significantly improved QoL in vitiligo patients, with improvement

observed in five of six DLQI domains. Treatment-induced changes in the VAS score showed a significant decline in life disturbance and improvement in life satisfaction. Multivariate analysis revealed that sex and treatment duration were independent factors influencing treatment outcomes. The study concluded that treatment of vitiligo with excimer laser can positively influence patients' QoL. Patients with multiple focal lesions should be treated by excimer laser even if some lesions may not show significant clinical improvement.

In June 2015, Byun et al[73] evaluated the effectiveness of using the 308nm laser for treating alopecia areata (AA). One alopecic patch was divided into control and treated sides in 10 patients with AA. Then, 308-nm excimer laser therapy was administered twice a week for 12 weeks. Photographic assessments by both dermatologists and individuals of the general population showed objective improvements after excimer laser therapy. On the treated side, the hair count and hair diameter had statistically increased after treatment. However, only the hair diameter was found to be significantly high in the treated half when it was compared with the control side. The conclusion was that the 308-nm excimer laser has a therapeutic effect on AA, which is proven by photograph and phototrichogram analysis by a side-by-side comparison.

In 2015 the efficacy of monochromatic excimer light compared to the efficacy of topical combination therapy of vitamin D3 analogue and steroid in the treatment of nonsegmental vitiligo was explored by Latif and Ibrahim[52]. Forty-four patients participated in the study; two lesions from each patient were divided randomly into two groups. Group A was treated with daily topical combination of calcitriol and betamethasone and group B was treated with biweekly sessions of MEL for 3 months. Both treatment modalities showed significant improvement at the end of the study, but without significant differences in both groups. There was a significant difference between both groups regarding the onset of repigmentation (p-value < 0.05), whereas group B showed early sign of repigmentation in first 4 weeks of treatment in 16 patients versus 7 patients in group A. Both treatment modalities offered encouraging results and both are promising lines for the treatment of vitiligo.

In April 2016, Arakawa et al evaluated the use of 308 nm excimer laser for the treatment of alopecia universalis that was resistant to other treatments. Eleven treatment-resistant AU patients were treated with a 308-nm excimer light at 2-week intervals for more than 16 sessions. Four patients achieved good responses and two patients exhibited poor responses. Three patients had Japanese skin type 1 and all of them achieved good responses. The radiation dose was increased until the patients exhibited marked erythema. The patients with Japanese skin type 3 who achieved good responses exhibited strong pigmentation at the irradiated sites. In conclusion, 308-nm excimer light therapy has significant effects on some AU patients who are resistant to other treatments and may be an alternative therapeutic option for AU. During the treatment of AU, high doses of radiation should be administrated until a strong inflammatory skin reaction is seen.

In Aug 2016, Shroff et al[69] published on the effectiveness of the 308nm laser for the treatment of chronic hand and foot eczema (CHFE). The study is a retrospective chart review conducted on 30 patients with recalcitrant CHFE (19 with hand involvement, four with foot involvement, and seven with both) treated twice weekly with excimer laser (308 nm) single wavelength ultraviolet (UV) B radiation between January 2013 and December 2014. Improvements in clinical scores included a 69% reduction in average physician's global assessment (PGA) scores (from 2.77 at baseline to 0.87 after treatment, $P < 0.0001$) with a parallel reduction in average modified total lesion/symptom scores of 70% (from 10.2 to 3.1, $P < 0.0001$). The study concluded that the excimer laser shows excellent and sustained efficacy for the treatment of CHFE.

In December 2016, Abrouk et al evaluated the safety, efficacy, and patient acceptability of excimer laser for the treatment of psoriasis. The 308 nm excimer laser is a widely used device throughout the field of dermatology for many diseases including psoriasis. A literature search on PubMed was used with combinations of the terms "excimer", "excimer laser", "308 nm", "psoriasis", "protocol", "safety", "efficacy", acceptability", "side effects", and "dose". The search results were included if they contained information pertaining to excimer laser and psoriasis treatment and description of the safety, efficacy, and patient acceptability of the treatment. The result as that 308 nm excimer laser is generally safe and well tolerated with minimal side effects including erythema, blistering, and pigmentary changes. It has a range of efficacies depending on the protocol used with several different treatment protocols, including the induration protocol, the minimal erythema dose protocol, and the newer minimal blistering dose protocol. Although the excimer laser is not a first-line treatment, it remains an excellent treatment option for psoriasis patients and has been demonstrated to be an effective treatment with little to no side effects.

In February 2017, Y. Fa et al evaluated the efficacy of 308-nm excimer laser for the treatment of vitiligo in Chinese patients. A total of 979 Chinese patients (3478 lesions) with progressive-stage vitiligo who had received 308-nm excimer laser treatment were recruited from the vitiligo clinic of Shandong Provincial Hospital of Dermatology &Venereology from 2012 to 2014. Efficacy of treatment was evaluated at the end of session by two independent dermatologists based on the before and after images taken. Repigmentation was graded on a 4-point scale: grade 1, poor repigmentation (0-25%); grade 2, moderate repigmentation (26-50%); grade 3, good repigmentation (51-75%); grade 4, excellent repigmentation (76-100%). The mean grade of repigmentation was 2.29, 44.22% showed less than 25% repigmentation, 16.27% showed 26-50% repigmentation, 5.95% showed 51-75% repigmentation and 33.55% showed more than 76% repigmentation. The repigmentation of facial lesions was better than lesions located elsewhere ($P < 0.0001$), the best response was noted in the periorbital region, while lesions on hands and feet showed poor repigmentation ($P < 0.0001$). The degree of repigmentation was negatively correlated with disease duration ($r = -0.268$, $P < 0.001$), age ($r = -0.095$, $P < 0.001$) and shape of lesions ($r = -0.114$, $P < 0.001$), whereas it was positively correlated with treatment frequency ($r = 0.270$, $P < 0.001$). Lesions with concurrent poliosis were more likely resistant to treatments. In conclusion 308-nm excimer laser is an effective and safe treatment in Chinese vitiligo patients.

In June 2017, Eldin et al compared (311–312 nm) narrow band Ultraviolet-B phototherapy and (308 nm) monochromatic excimer light phototherapy in treatment of Vitiligo in a histopathological study. Thirty subjects with non-segmental vitiligo lesions were treated twice a week for 6 weeks with 308-nm MEL, while NB-UVB was used to treat lesions contra laterally. Skin biopsies were taken from lesional areas before and after 6 weeks of treatment by either modality. It was prepared for light microscopy and immune-histochemical study. All lesions before treatment had labeling index (number of pigmented cells/nonpigmented cells) of 0.0 (0%). After treatment the LI for MEL was 4.2±2.6, while for NBUVB LI it was 0.3±0.7. MEL showed higher statistical significance regarding increase of basal pigmented cells, and significant decrease in vacuolated keratinocytes and basal membrane thickness than NB-UVB. Although NB-UVB is considered as treatment of choice for vitiligo, MEL is acknowledged as an effective treatment modality for vitiliginous lesions that induces more repigmentation than NB-UVB, and more rapidly, as confirmed by the study.

In July 2017, Serena et al treated a 38 year old male affected by pustule palmar psoriasis which is a chronic, stubborn pathology, difficult to manage with a high recurrence rate. A focused narrowband UVB treatment, using a monochromatic excimer light device developed to deliver a 308 nm radiation only to the affected areas,

thus sparing the unaffected surrounding skin was used to treat the lesions. The therapeutic procedure scheduled two sessions in a week for the first four weeks of treatment, and then one session in a week for the rest of the treatment. At week 6 (10 treatments), the clinical picture was substantially improved, showing a clear reduction of inflammation, erythema, desquamation, and the complete disappearance of pustules. The treatment was interrupted at week twelve (16 total sessions) when the complete resolution of the disease was seen. During the entire treatment time, no side effects or adverse events were noted. Only a slight, transient erythema appeared after each of the first four sessions, however leading to no harms or discomfort for the patient. Since treatment discontinuation, the subject was monitored to evaluate the possible recurrence of psoriasis. However, after 12 weeks without any treatment, no lesions were present to date. In conclusion the monochromatic excimer light (MEL) device delivers a UVB wavelength at 308 nm only to the lesional skin, and seems particularly effective for variants of psoriasis where the involvement of the skin is lower than 20-25% of the total body surface. Its high potency (up to 4.5 J/cm2) and subsequently the need for short time of irradiation, together with the possibility to schedule just 1 session per week, makes MEL mostly appreciated to a large part of patients, thus increasing treatment compliance, which is particularly useful when we have to deal with long-lasting therapeutic protocols. Finally, the possibility to focus the radiations on skin lesions reduces the risks of acute and chronic side effects in the uninvolved safe skin.

In August 2017, Liu et al investigated the efficacy of 308-nm excimer laser in the treatment of OLP oral lichen planus. The traditional narrow spectrum UVB treatment has an established efficacy on skin lichen planus, and high safety. However, most of ultraviolet phototherapy devices have a huge volume, thereby cannot be used in the treatment of OLP. Lymphocytic infiltration is evident in the lesions of lichen planus, and the direct irradiation of 308-nm excimer laser can induce apoptosis of the T lymphocytes in skin lesions, thereby has a unique therapeutic effect on the diseases involving T lymphocytes. A total of six OLP patients were enrolled into this study, and further pathological diagnosis was conducted, then 308-nm excimer laser was used in the treatment. The efficacy of 308-nm excimer laser in the treatment of OLP was satisfactory. The clinical symptoms of five patients were significantly improved. In two patients, the erosion surface based on congestion and the surrounding white spots completely disappeared, and clinical recovery was achieved. Three patients achieved partial remission, that is, the erosion surface healed, congestion and white spot area shrunk by more than 1/2 of the primary skin lesions. In the remaining one patient, the erosion surface had not completely healed after treatment, and congestion and white spot area shrunk by less than 1/2 of the primary skin lesions. Only one patients had developed mild pain during the treatment, and this symptom alleviated by itself. The 308-nm excimer laser therapy can serve as a safe and effective treatment for OLP.

In August 2017, Jung et al evaluated the use of 308 nm excimer laser for the treatment of Laser Therapy-Induced Punctate Leukoderma. Punctate leukoderma presents as numerous, distinct, round or oval depigmented spots. Recently, laser therapy-induced punctate leukoderma associated with various Q-switched laser and carbon dioxide laser have been reported. A 25-year-old man presented with numerous, discrete, round, confetti-like, depigmented macules on his left neck. He had undergone 3 sessions of 532-nm Q-switched Neodymium: Yttrium-Aluminum-Garnet laser treatment for café-au-lait macules three years ago. After the last laser treatment session, the punctate leukoderma had been developed. The treatment was started with the 308-nm excimer laser twice a week. After 7 months of treatment duration, complete repigmentation was achieved without serious adverse effects. The authors recommended that the 308-nm excimer laser as an effective treatment modality for laser therapy-induced punctate leukoderma.

In September 2017, Mlacker et al evaluated the use of excimer and other light based therapies for the treatment of Alopecia Areata. As per the study although traditionally used for the treatment of inflammatory diseases of the skin such as psoriasis and vitiligo, excimer lasers may be additionally employed to treat AA, as they may trigger apoptosis of T cells. These lasers are also thought to induce immunological action through water-soluble mediators, such as IL-4, IL-10, prostaglandin E2, platelet activating factor, histamine, and cis-urocanic acid.

As per Fritz et al in January 2018, Use of the 308 nm Excimer laser to treat hypopigmentation and vitiligo is usually superior to conventional ultraviolet (UV) therapy with regard to results and safety. It is particularly advantageous because specific areas of skin can be targeted without burdening the rest of the skin. Fewer sessions with lower cumulative doses are required. Various combination therapies can improve the outcome; selection criteria such as early initiation of treatment and more frequent sessions with shorter intervals make it easier to decide which patients should be treated and how to achieve the greatest benefit.

In January 2018, Fritz et al evaluated the 308 nm Excimer laser for the treatment of psoriasis and inflammatory skin diseases. The conclusion was the 308 nm Excimer laser enables not only a more effective and safer UVB therapy than classical UV phototherapy, but also targeted irradiation in higher doses with a lower cumulative load, which results in faster healing of mainly circumscribed skin changes. This also applies to therapy-resistant residual lesions which, despite systemic therapy, did not diminish. Combination therapies usually improve the result and enable the dose of UVB and systemic medication to be reduced. Excimer laser therapy can be used for an increasing number of skin diseases, especially those that respond to phototherapy or photochemotherapy.

In February 2018, Yang et al used 308 nm excimer laser for the treatment of Hypopigmented Mycosis Fungoides in a 10-year-old Korean boy. The conclusion was that the 308 nm excimer laser could be a good option for the treatment of HMF with a limited distribution.

In January 2019, Shah et al to evaluate the efficacy of monochromatic excimer light (MEL) in treating Halo Nevus. A total of 29 patients with 10 males and 19 females completed the study. Outstanding response was noticed in 14 patients (48.2%), whereas 6 (20.6%) patients showed excellent improvement. Only 2 (6.8%) patients showed no response after 10 consecutive sessions. MEL is a noninvasive procedure, which results in excellent repigmentation of HN without scarring.

In May 2019, Lee et al conducted a meta-analysis of various studies having total 1499 patients to estimate the treatment responses to both TCI monotherapy and TCI accompanied by phototherapy for vitiligo, based on relevant prospective studies, and to systematically review the mechanism of action of TCIs for vitiligo treatment. For TCI plus phototherapy (308nm excimer laser), an at least mild response to TCI plus phototherapy was achieved in 89.5%(95%CI, 81.1-97.9%) of patients, and a marked response was achieved in 47.5%(95%CI, 30.6-64.4%) of patients.

In July 2019, Armenta et al, studied the use of excimer laser in the treatment of patients with dysplastic nevi (DN) or other conditions which can put them at a higher risk of developing skin cancer. Targeted phototherapy with a 308-nm excimer laser may be a safer and equally effective alternative to generalized phototherapy in the treatment of early-stage MF. This case report demonstrates its efficacy and advantages over traditional generalized phototherapy.

The summary of clinical studies, excluding case studies, of the 308-nm laser treatment for psoriasis include a 6-patient comparative trial (Bonis et al); a 21-patient prospective trial (Novak et al); a 16-patient controlled trial (Trehan et al); a 92-patient, 5-site multicenter trial (Feldman et al); a 15-patient controlled, blinded trial (Trehan et al); a 14-patient controlled trial (Taneja et al); a 28-patient trial (Fikrle et al); a 142-patient prospective trial (Gerber et al); a 16-patient prospective trial (Pahlajani et al); and a 35-patient retrospective trial (Morison). These studies are well-defined and well-conducted, as evidenced by their publication in highly respected peer-review journals. These studies provide statistically significant evidence that the 308nm light energy alters the physiological course of psoriasis and that alteration reduces the psoriatic condition, thus improving the health outcome of the patient.

There is a strong basic scientific foundation in the literature that UVB light is effective in treating psoriasis; furthermore, that narrowband UVB light is more effective, and finally, that super narrow band UVB light at 308nm enables a more potent delivery of the antipsoriatic action of the light energy at that wavelength spectrum.

b. As per National Medical Associations and other Technology Evaluation Bodies

In 2002, the Current Procedural Terminology (CPT) Advisory Panel of the American Medical Association (AMA) endorsed the laser treatment of psoriasis and, as a result, the AMA CPT Editorial Panel established three new CPT codes (96920, 96921 and 96922), effective January 1, 2003.

The American Academy of Dermatology's (AAD) representative to the AMA CPT advisory committee, Alan S. Wirtzer, MD, has stated that "in [the advisory committee's] deliberations it was necessary to evaluate the clinical efficacy of the devices in question and only after considerable review of the available literature, were we convinced that such treatments are beneficial to our patients." [Appendix A]

The National Psoriasis Foundation (NPF) issued a position statement on laser therapy for psoriasis in which they stated: "Because phototherapy is well accepted... these laser treatments are not considered investigational. They are medically effective and FDA-approved. The NPF encourages all health plans to include laser treatment as a covered benefit for their enrollees." [Appendix B]

The Chairman of the Psoriasis Task Force of the American Academy of Dermatology (AAD), Mark Lebwohl, MD, Professor and Chairman of the Department of Dermatology at the Mt. Sinai Hospital in New York City, supported the NPF endorsement of laser therapy for localized psoriasis. Dr. Lebwohl further stated that, in his assessment, "this treatment is not investigational." [Appendix C]

The President-Elect [at the time] of the American Society of Dermatologic Surgery, Roy G. Geronemus, stated that "laser phototherapy offers patients with localized disease a safe, effective, and quick treatment while offering a significant remission. The laser offers a new therapeutic opportunity to patients who fail older, conventional therapies." [Appendix D]

In November 2003, the American Academy of Dermatology issued the "AAD Consensus Statement on Psoriasis Therapies"[19] by JP Callen et al. This Statement indicates that "mild" disease, based on limited body surface area involvement, may still warrant phototherapy if not responsive to topical, e.g. that limited disease can be considered moderate for the purposes of selecting a therapy. The Statement identifies targeted phototherapy as an available therapy option for moderate disease.

In April 2004, the American Academy of Dermatology published a Periodic Synopsis on Psoriasis[20], reflecting (in the words of the American Academy of Dermatology) "the best available data at the time the report was prepared) written by J Koo, E Lee, CS Lee and M Lebwohl. The authors comprehensively reviewed articles on psoriasis published during the past 10 years in peer-review journals, and reported their assessment of the state of knowledge on psoriasis epidemiology, pathogenesis, precipitation/exacerbation, pediatric considerations, therapy, combination therapy, psychosocial factors and cost of care. In this definitive report, the 308-nm excimer laser is reported to be a safe and effective therapeutic modality that can effectively clear localized plaque type psoriasis in fewer treatments with an overall lower cumulative dose compared with standard phototherapy, and allows specific targeting of affected sites without needles or exposure of unaffected skin.

In February 2007, Pariser et al[21] published an article summarizing the conclusions of an expert task force of the National Psoriasis Foundation Medical Board on the clinical consensus on plaque psoriasis disease severity. The consensus statement is intended to assist medical professionals and insurance payers in understanding categorization of patients with psoriasis and choosing appropriate therapies for these patients. This consensus statement identifies excimer laser treatments as an appropriate therapy for localized plaque psoriasis.

In 2019, the American Academy of Dermatology[80], published the Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy, discussing the use of ultraviolet (UV) light therapy for the treatment of patients with psoriasis. The authors evaluated available evidence based on a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals. This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies. Evidence was graded using a 3-point scale based on the quality of methodology as follows:

I. Good-quality patient-oriented evidence.
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, or case studies.

Recommendation	Recommendation No.	Level of evidence
Targeted UVB for adult psoriasis	3.1	I-II
Dose • 2-3 times/wk vs 1-2 times/wk • Initial dose based on minimal erythema dose	3.2 3.3	I I

Comparison • Excimer laser vs excimer light vs NB-UVB	3.4	I
Special psoriasis type • Excimer laser and light for palmoplantar psoriasis	3.5	I-II
• Excimer laser and scalp psoriasis	3.7	II-III
Combination • Excimer laser + topical therapy	3.6	II

Clinical recommendations were developed on the best available evidence tabled in the guideline ranked by:

A. Recommendation based on consistent and good-quality patient-orientated evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion or case studies.

Strength of recommendations for targeted UVB		
Recommendation No.	**Recommendation**	**Strength of recommendation**
3.1	Targeted UVB phototherapy, including excimer laser (308 nm), excimer light (308 nm), and targeted NB-UVB light (311-313 nm), is recommended for use in adults with localized plaque psoriasis (<10% BSA), for individual lesions, or in patients with more extensive disease	A
3.2	To achieve maximal efficacy, treatment with targeted UVB phototherapy for adults with localized plaque psoriasis should be carried out 2-3 times/wk rather than once every 1-2 wk	A
3.3	The starting dose for targeted UVB phototherapy for adults with localized plaque psoriasis can be determined on the basis of the MED or by a fixed dose or skin phototype protocol	A
3.4	An excimer laser (308 nm) is more efficacious than an excimer light (308 nm), which is more efficacious than localized NB-UVB light (311-312 nm) for the treatment of localized plaque psoriasis in adults	B
3.5	Targeted UVB phototherapy, including excimer laser (308 nm) and excimer light (308 nm), is recommended for use in adults with plaque psoriasis, including palmoplantar psoriasis	A

3.6	Excimer laser (308 nm) may be combined with topical corticosteroids in the treatment of plaque psoriasis in adults	B
3.7	Excimer laser (308 nm) is recommended in the treatment of scalp psoriasis in adults	B

BSA, Body surface area; *MED*, minimal erythema dose; *NB*, narrowband; *UVB*, ultraviolet B.

The guidelines were developed in accordance with the AAD "Administrative Regulations for Evidence-based Clinical Practice Guidelines, which included the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors. The guidelines acknowledge the "breakage of strands of DNA in T lymphocytes and expression of mitochondrial proteins related to cell death after exposure to the 308-nm laser". This action results in "T-cell depletion accompanied by decreased epidermal proliferation". The guidelines state that the excimer laser "has the advantage of treating only involved skin, therefore minimizing potential risks of exposing normal-appearing skin to UV radiation".

In April 2011, the Spanish Psoriasis Group[40] declared a consensus statement that NBUVB is more effective and has less erythemal radiation than UVB broadband. NBUVB therapy is a "safe and effective treatment for most patients with moderate and severe psoriasis and, in fact, represents a good alternative for many patients in whom other treatments are not feasible or pose an excessive risk."

Numerous reviews by healthcare payor organizations have resulted in positive medical coverage policies.

3. Improvement the net health outcome

Short-term side effects of 308-nm laser phototherapy have been reported by Feldman et al[12] to include erythema (51%), blisters (45%), hyperpigmentation (38%), erosion (25%), pain (10%), sunburn sensation (7%), scaling (6%), itching (5%), tenderness (3%), flaking (2%), peeling (2%), vesicles (2%), flare of disease (<1%), scab (<1%), and weeping lesions (<1%). Side effects were generally well tolerated, and no subject discontinued treatment because of adverse events.

Feldman et al further commented that "by treating only lesional skin, an even greater benefit/risk is expected because there will be less risk to the uninvolved skin. In addition, this allows higher doses to be used initially on the psoriasis plaques, resulting in faster clearing and fewer exposures."

Taneja et al[14] reported with induration-based dosimetry that the only adverse event was a mild sunburn-like reaction in the focal areas in 2 subjects (14%) after 1 treatment. This resolved spontaneously after skipping a treatment. There were no instances of blistering or Koebner phenomenon; a tanning reaction was observed in 4 subjects that faded 2 to 4 weeks post-last treatment; post-inflammatory hyperpigmentation was observed in 8 subjects that resolved gradually over 2 to 6 months.

Gerber et al[16] reported with their standard protocol observing blistering at least once in 40% of the patients, and 26% in that group had erosions and pain. With their induration protocol, blistering was observed in only 8% of the patients. These side-effects were reported to be well-tolerated by patients, and that therapy was not terminated for this reason.

Studies have shown that carcinogenicity of different UV therapies increase in parallel with the cumulative UV dose during life.22 Targeted phototherapy, such as with the XeCl laser, results in sparing the surrounding

normal skin from unnecessary (potentially carcinogenic) UV radiation exposure,6 as opposed to traditional, non-targeted phototherapy, which exposes normal skin to potentially harmful UV energy. Furthermore, Novak et al[6] reported that the cumulative dosing was 6 times less with the XeCl excimer laser than with narrowband UVB. They postulated that the lower therapeutic cumulative dose therefore involves a lower risk of carcinogenesis, although no studies have confirmed this hypothesis. Gerber reported that the cumulative UVB dose required to heal psoriatic patients with the excimer laser was 50% lower than with narrowband UVB, but, at the same time, a 100% lower UVB dose is applied with the excimer laser to healthy skin as healthy skin is spared the treatment in the first place.

The body of clinical evidence and scientific literature supports the conclusion that the beneficial effects on health outcomes outweigh any harmful effects on health outcomes.

4. The technology must be as beneficial as any established alternatives.

Established alternative therapies for mild-to-moderate psoriasis include topical therapy and UV phototherapy. A direct comparative trial of 308-nm therapy versus narrowband UVB by Bonis et a[5] showed that the 308-nm therapy achieved clearance similar to narrowband UVB but with fewer treatments, specifically in only 8 treatments on average with the 308-nm laser versus 30 treatments with narrowband UVB. In fact, the number of treatments was 3.6 times less with the laser than with narrowband UVB, providing the patients with a significantly more efficient alternative treatment.

Efficacy of the variety of topical therapies is well established and has been reported extensively in the literature, as has the effect of placebo treatments. Rodewald et al[23] published a meta-analysis of studies reporting results with topical therapy, phototherapy and combination therapy, and compared that to the reported results with 308-nm UVB laser treatment. This study reported that:

"A greater percentage of patients achieved 75% improvement with the UVB laser treatments than was reported for other forms of phototherapy or systemic therapy with acetretin or low dose cyclosporine, and did so more rapidly. The UVB laser study patients achieved the 75% improvement endpoint in an average of 46% fewer treatments than was observed in other phototherapy studies. Laser treatment and topical calcipotriene had similar efficacies, and both were more effective than topical tazarotene or topical fluocinonide. As compared to topical therapies, the time to achieve 75% improvement favored the UVB laser. 308nm laser treatments for psoriasis are clearly more effective than placebo and are comparable to or more effective than many other standard treatments for psoriasis."

Koo and Lebwohl[24] reported in a literature review of remission rates that data suggest that UVB therapy results in longer remissions when conducted according to established protocols in a dermatologist's office. Taneja et al[14] reported a mean remission duration of 6 months with the 308nm excimer laser (using 50% modified PASI score improvement as the benchmark). Feldman[25] reported in a follow-up study on 51 patients a mean relapse-free period of 16 weeks with the 308nm excimer laser. Trehan and Taylor[13] reported 3.5-month mean remissions with the 308nm laser treatment (using a PASI-75 benchmark). These remission durations with the 308-nm laser treatment compare favorably with the published relapse rates of topical therapies and systemics as reported by Koo and Lebwohl[22].

Gerber et al[16] concluded that the excimer laser-generated 308-nm UVB treatment is one of the most effective treatment forms for moderate and chronic forms of psoriasis, and that UVB laser treatment for localized

psoriasis has considerable advantages over current topical and conventional UVB treatment. They furthermore stated that their study has shown the excimer laser to be effective in treating thick, scaled plaques on the knees and elbows, which are often resistant to any conventional treatment.

A peer-reviewed article by Marchetti et al[26] compared the clinical effectiveness and cost effectiveness (from a payer perspective) of various established treatment alternatives for mild to moderate plaque psoriasis resistant to topical therapy. The authors conducted a cost- effectiveness analysis using well-established disease intervention modeling techniques and established benchmarks for intervention efficacy of the various treatment modalities. This study concluded that "the addition of the excimer laser to the rotational mix of second-line therapies for patients with mild-to-moderate plaque psoriasis results in additional and substantial clinical benefits without incremental cost to payers. This finding can provide guidance for all those interested in disease management because it suggests that providers and patients can gain an advantage when the intervention is appropriately utilized. Additionally, because the intervention is associated with fewer treatment sessions and treatment days compared to other standard therapy and is less troublesome to use, there is an opportunity to increase patient satisfaction, which contributes to plan satisfaction. Finally, because total expected annual per-patient costs are equivalent with or without the excimer laser included as part of comprehensive care, payers bear no incremental financial risk for laser utilization. . . . all these considerations support decisions to utilize and reimburse 308-nm excimer laser procedures as a part of the second-line mix of therapy for plaque psoriasis resistant to first-line topical therapy."

These data indicate that 308-nm excimer UVB therapy improves the net health outcome as much as, or more than, established alternatives.

5. Improvement must be attainable outside the investigational settings.

Clinical investigations of the 308-nm UVB excimer laser therapy were conducted under the usual conditions of medical practice; thus, patients are expected to achieve similar results when receiving this treatment in the clinical setting.

Typically, in the clinical setting, psoriasis patients will be treated initially with topical therapy as a first-line treatment. The 308-nm therapy will be generally considered as a treatment option for patients in whom topical therapy has failed.

Additionally, in the clinical setting, it is not practical to treat more than 20% body surface area of psoriasis, because of the extended treatment time required due to the relatively small treatment-spot size. Investigations generally reflected this clinical setting reality, limiting eligible study patients to those with less than 20% body surface area of psoriasis.

Over 300,000 laser psoriasis procedures are being performed every year in the United States. This is further evidence that the procedure is effectively performed outside of investigational settings.

V. PLACE IN THERAPY

The body of evidence provided herein supports the use of the 308-nm excimer laser as safe and effective for localized plaque-type psoriasis resistant to other first-line therapies, such as topical creams and ointments.

The ideal treatment candidate for 308nm UV laser light therapy would be a patient with mild or moderate plaque psoriasis covering less than 20% of body surface area for whom first-line therapy, such as topicals, has been unsuccessful. (the 20% BSA is achievable with more effective laser systems, generating faster pulses and faster treatment)

VI. COMBINATION THERAPY

a. Topicals

Topical agents form the mainstay of treatment in psoriasis and all other treatment modalities are often used with concomitant topical therapy. Emollients increase the transmission of UV radiation by altering the optical properties of psoriatic skin lesions and improving therapeutic efficacy[87,88]. It is important to pay attention to the application of sunscreens or salicylic acid containing preparations that may interfere with the penetration of UV radiation. UV blocking properties may be used to cover uninvolved skin with preparations such as zinc oxide to prevent unnecessary exposure and adverse effects[81].

Many studies have consistently reported that combination interventions of topical therapy and phototherapy were superior to monotherapies[76]. Phototherapy induces a predominantly perifollicular pattern of repigmentation, whereas topical agents exhibit a diffuse type, acting synergistically when combined[75].

Passeron et al[45] first explored this technique utilizing topical tacrolimus for the treatment of vitiligo. A comparative, prospective, randomized, intraindividual study on 14 patients aged 12-63, Fitzpatrick skin types II to IV was developed. The lesions were randomly assigned to Group A, combination therapy, Group B, laser only therapy. Forty-three lesions were treated (23 in group A and 20 in group B). Repigmentation was observed in all patients in group A and in 85% of group B lesions. Repigmentation was not observed in the untreated control group. A repigmentation rate of 75% or more was obtained in 70% of the Group A lesions and 20% of the group B lesions. The mean number of sessions necessary for an improvement of repigmentation was 10 in group A and 12 in group B. The study demonstrated the combination treatment of 0.1% tacrolimus ointment plus the 308-nm excimer laser is superior to 308-nm excimer laser monotherapy for the treatment of UV-resistant vitiliginous lesions ($P<0.002$). The efficacy and the good tolerance of the 308-nm excimer laser in monotherapy for treating localized vitiligo were also confirmed, but this treatment regimen should be proposed only for UV-sensitive areas.

Also in 2004, Kawalek et al[46] published also published on the efficacy of utilizing topical tacrolimus in combination with the 308nm excimer laser for the treatment of vitiligo. Eight subjects diagnosed with vitiligo (24 patches) received treatment three times per week for 24 treatments (10 weeks) in this double-blind, placebo-controlled study. In addition, topical tacrolimus 0.1% ointment and a placebo were applied to randomized patches twice daily throughout the length of the trial. Fifty percent of patches treated with combination therapy achieved 75% repigmentation compared with 20% for the placebo group, i.e. laser alone. Subjects who responded successfully repigmented faster (19%) with combination therapy compared with the excimer alone. Three subjects experienced transient hyperpigmentation in lesions treated with combination therapy. The study demonstrated that combining topical immunomodulators with known phototherapeutic modalities may represent a key advancement in the treatment of the disease.

In 2008, Sassi et al[49] published a parallel-group randomized controlled trial comparing the effectiveness of the 308nm laser alone versus in combination with topical hydrocortisone 17-butyrate cream in patients with vitiligo unresponsive to previous treatment with topical steroids or narrow-band ultraviolet (UV) B phototherapy. A total of 84 patients (44 women and 40 men, mean age 44 years) were randomized to the laser therapy twice weekly alone or in combination with topical hydrocortisone 17-butrate cream twice daily for three periods of 3 weeks followed by a 1-week steroid-free interval. A total of 76 (90%) patients completed the study. In an intention-to-treat analysis, seven [16.6%; 95% confidence interval (CI) 5.3-27.8%] patients in the excimer monotherapy arm and 18 (42.8%; 95% CI 27.8-57.8%) in the combination arm showed > or = 75% reduction of vitiligo lesions at 12 weeks (chi(2) test 6.89, P = 0.0087). Clearance was observed in two (4.7%; 95% CI 1.6-11.2%) and nine (21.4%; 95% CI 9.0-33.8%) patients, respectively (Fisher's exact test P = 0.04). A significant difference also emerged for PGA scores, while no difference was documented for Skindex-29. It was concluded that Recalcitrant vitiligo of the face and neck may benefit from the combination of excimer laser phototherapy with topical hydrocortisone 17-butyrate cream.

In October 2010, Asawanonda et al[47] compared the efficacy of 308nm excimer laser plus topical tetrahydrocurcuminoid with that of UV monotherapy in the treatment of vitiligo. Ten subjects received treatment twice per week for 12 weeks. The study outcomes showed statistically significant repigmentation in both groups. The overall degree of repigmentation was slightly better in the combination group at 8 and 12 weeks (p = 0.078 and 0.158 respectively). The study concluded that targeted narrowband UVB phototherapy plus topical tetrahydrocurcuminoid cream was slightly more effective than targeted narrowband UVB monotherapy for vitiligo located in UV-sensitive areas; however, the differences in degrees of repigmentation did not reach statistically significant levels.

In March 2011 Rogalski et al[56] reported on the treatment of plaque-type psoriasis with the 308nm excimer laser in combination with dithranol or calcipotriol. This within-patient comparison study evaluates the response rates of plaque-type psoriasis after treatment with topical only (dithranol or calcipotriol), laser only, and combination therapy with topical medication and laser. A total of 61 patients with psoriatic plaques located at symmetric body areas (PASI_6) were screened, 59 were enrolled, 54 completed treatment and 45 completed the 6 months follow-up. Treatments with the excimer laser were performed twice weekly until resolution or a maximum of 15 treatments. Each ointment was applied on one of the test lesions, which had to be at least 10 cm apart from each other. At the end of the treatment phase only one patient in both topical therapy regimens met the criteria of partial clearance (modified PASI_2). The combined therapies resulted in 23 cases of partial clearance in both treatment arms. Four areas treated with calcipotriol, respectively six areas treated with dithranol resulted in total clearance at the end of the treatment phase. The average reduction of modified PASI scores was higher in combination than in topical treatment alone (49.8% calcipotriol + excimer versus 22.9% calcipotriol, 49.7% dithranol + excimer versus 26.8% dithranol). After six months there was a total clearance of 30.5% dithranol + excimer. The results concluded that the treatment of plaque-type psoriasis with laser in combination with topical treatment is a safe and effective therapy. The best long-term results can be obtained by the application of dithranol and excimer laser.

Also in 2011, Mouzakis et al[54] reported on the use of the 308nm laser in conjunction with topical calcipotriene for the treatment of facial vitiligo. Three patients with previous failure to a variety of topical treatments including steroids and calcipotriene participated. Laser therapy was performed twice weekly in conjunction with 0.005% calcipotriene topical administered twice daily. Two patients achieved greater than 75%

repigmentation after 22 treatments or less (11 weeks) and one patient achieved 75% repigmentation after 40 treatments (20 weeks).

In June 2012, Dong et al[50] compared the clinical efficacy and safety of combining flumetasone ointment with 308-nm excimer laser therapy vs. 308-nm excimer laser monotherapy for the treatment of psoriasis vulgaris. Forty patients with psoriasis vulgaris were recruited; 20 were treated with flumetasone ointment plus 308-nm excimer laser therapy, and the other 20 received only excimer laser monotherapy. The flumetasone ointment was applied topically twice a day, and laser treatments were scheduled twice weekly for a total of 10 treatments. Of the 40 patients who received and completed the entire course of therapy, the psoriasis area and severity index score was improved by 82.51 ± 11.24% (combination group) and 72.01 ± 20.94% (laser group) respectively ($P > 0.05$), and the average cumulative dose was 5.06 2.20 j/cm2 in the combination group and 7.75 2.25 j/cm2 in the laser-only group, respectively ($P < 0.05$). The clinical data suggest that combination treatment using flumetasone ointment and a 308-nm excimer laser is superior to laser monotherapy for treatment of psoriasis vulgaris. The combination therapy can increase effectiveness and decrease the total laser dose, thus potentially reducing side effects.

In August 2012, Wong et al[57] published a case series on psoriasis and long-term maintenance using 308nm excimer laser, clobetasol spray and calcitriol ointment. Two patients applied clobetasol spray twice daily for 4 weeks; for weeks 5-8, calcitriol ointment was applied twice daily and week's 9-12 clobetasol spray and calcitriol ointment was applied twice daily. Patients were treated with the laser twice weekly until they reached 75% reduction in Psoriasis Area and Severity Index score (PASI 75). Patient 1 started with PASI 14.6 and reached PASI 75 in 10 treatments. After 12 treatments, PASI 1.9 was achieved. The second patient started treatment at PASI 9.6 and reached PASI 75 after 10 treatments; sixteen treatments were needed to achieve PASI 1.8.

In 2014 Tang et al[77] published a randomized, open and self-control trial in 36 selected patients to compare the differences of clinical efficacy and safety of treatment of stable psoriasis vulgaris with calcipotriene ointment in combination with 308 nm excimer laser to 30 nm excimer laser alone. The skin lesions from these patients with stable psoriasis vulgaris were divided into two sides along the midline of torso, one side was treated with 308 nm excimer laser, 2 times/week, at meantime Calcipotriene was applied externally, 2 times/day (treatment group); the other side was given 308 nm excimer laser alone, 2 times/week, the treatment period was 6 weeks (control group). 32 of 36 patients with stable psoriasis vulgaris completed study, effective rates in two groups were better on week 6 (84.37%, 56.25%) than on week 4 (53.12%, 37.5%) and on week 2 (31.25%, 18.75%) ($P < 0.05$). Effective rate on week 6 in control group (56.25%) was lower than treatment group (84.37%) ($P < 0.05$). The two groups showed that PASI scores on weeks 2 and 4 after treatment were significantly lower than before treatments ($P < 0.05$), and PASI scores on week 6 in treatment group was significantly lower than control group ($P < 0.05$). The study concluded that the treatment of psoriasis vulgaris with 308 nm excimer laser in combination with external application of Calcipotriene ointment can improve long-term treatment efficacy, decrease cumulative laser doses, and reduce adverse effects induced by laser irradiations.

Also in 2014, Matin[78] published a retrospective analysis on the effectiveness of the excimer laser for the treatment of vitiligo compared to a combination therapy of the excimer laser and 0.01% tacrolimus in an Iranian population. The authors reviewed the medical files of 150 patients with vitiligo who were referred to the Behsima Laser Center between April 2012 and April 2013. Seventy five patients who received combined

therapy of the 308 nm excimer laser and topical tacrolimus three times a week entered the study. Seventy-five controls with matched characteristics and who received only the excimer laser were also selected. In the combination therapy group, 33.3% (n: 25) showed 50-75% repigmentation and 49.3% (n:37) had more than 75% response to therapy, whereas among the patients in the control group 29.3% (n: 22) showed no repigmentation and only 8% (n: 6) demonstrated more than 75% repigmentation response. The higher efficiency of the combination therapy on repigmentation was statistically significant (P=0.006).

In 2015, Namazi and Shortorbani[55] evaluated the efficacy of topical ethyl vanillate for enhancing the effect of narrowband UVB against vitiligo. The goal was to investigate if oxidative stress were a triggering factor for the destruction of melanocytes in the epidermis, thus leading to vitaligo. A double blind randomized, placebo-controlled clinical trial using ethyl vanillate cream 20% was performed on 30 patients (23 females, 7 males) of generalized stable vitiligo (randomly selected). Patients randomly applied ethyl vanillate on an assigned lesion and a placebo on the opposite side lesion twice a day for 3 months while receiving NBUVB 2-3 times weekly for 12 weeks. Result showed 36.6% of lesions which were treated with ethyl vanillate showed a change in pigmentation (mostly mild clinically) compared with 13.3% in placebo side. The study concluded ethyl vanillate may serve as an adjunct therapy for the treatment of vitiligo, although changes in pigmentation are mild clinically.

In January 2016 Solimoan et al[72] compared the efficacy of combined topical antioxidant hydrogel and excimer light versus excimer light alone in treating vitiligo. Thirty patients were included in this comparative, prospective, randomized study. For each patient, at least 2-4 vitiliginous macules were randomly selected and treated while an untreated vitiliginous macule served as control. Lesions were divided into two groups: Group A received combination therapy of daily topical antioxidant plus excimer light, while Group B received only excimer light. Lesions were treated twice a week for a maximum of 24 sessions. Group A lesions showed significantly greater efficacy than group B ($p < 0.001$), especially on treating UV-sensitive lesions with no side effects.

In June 2016 Levin et al[53] published an open label pilot study of the 308nm excimer laser in combination with clobetasol spray and calcitriol ointment for the treatment of moderate to severe generalized plaque psoriasis. In this 12-week study, patients with moderate to severe psoriasis received twice weekly treatments with a 308-nm excimer laser combined with clobetasol proprionate twice daily for a month followed by calcitriol ointment twice daily for the next month. Of the 30 patients enrolled, 83% of patients (25/30) achieved PASI-75 [65-94%, 95% confidence interval (CI)] at week 12. For PGA, there was an estimated decrease of 3.6 points (3.1-4.1, 95% CI, $p < 0.0005$) by week 12. In conclusion, the combination of excimer laser with alternating clobetasol and calcitriol application has shown to be a promising combination of therapies for the treatment of moderate to severe generalized psoriasis.

In April 2016, Park et al[70] evaluated the clinical efficacy according to the duration of treatment and in vitro results of a combination therapy involving topical tacrolimus and an excimer laser in the treatment of vitiligo. In total, 276 patients with nonsegmental vitiligo were treated with an excimer laser twice weekly, or with tacrolimus ointment twice daily, or both. After adjusting for potential confounders, the combination of tacrolimus plus excimer laser was significantly more effective than either tacrolimus or excimer laser alone ($P < 0.001$ and $P < 0.01$, respectively) for the first 6 months. However, this superiority was not observed after the initial 6 months of treatment. In vitro, the combination of tacrolimus plus excimer laser led to a higher level

of melanogenesis than with either treatment alone. A combination treatment with topical tacrolimus and an excimer laser may be useful as an induction therapy for up to 6 months, but continuation of this therapy for > 6 months might not provide a better final outcome than monotherapy

b. Other Combination Therapies

In July 2006, Koo et al[66] published a study on the efficacy of alefacept in combination with Ultraviolet B phototherapy for the treatment of chronic plaque psoriasis. In the study, patients received us to 3 treatment courses (courses A, B and C) with each course consisting of alefacept 15mg administered intramuscularly once weekly for 12 weeks, following by a treatment-free observation period of at least 12 weeks. Patients were required to receive at least 8 doses of alefacept in the proceeding courses. One concomitant therapy of either phototherapy with narrow-band or broadband UVB administered 2-3 times per week, methotrexate, prednisone, systemic retinoids or topical treatment was allowed per course. At total of 449 patients received one or more doses of alefacept in course A, 340 in course B and 203 in course C. Twenty-four patients received alefacept in combination with UVB in course A, 21 in course B and 24 in course C. A patient was not required to maintain the same course of concomitant therapy for all three treatments. Results of the cohort analysis suggest that the combination of alefacept and UVB phototherapy is an effective treatment for chronic plaque psoriasis, with a majority of evaluated patients in each course of therapy experience 2 or more categories of PGA improvement from their course A baseline. The results of UVB cohort were better than those of other cohorts in the study, including alefacept monotherapy and alefacept in combination with retinoids or topical steroids The authors noted that, "the incremental efficacy obtained when combining alefacept and UVB may be a result of their different and possibly complementary modes of action on T cells within the skin, that is, alefacept has been shown to selectively reduce dermal CD4+ memory T cells, whereas UVB phototherapy reduces epidermal CD3+ cells.

In March 2008, Kircik et al[99] published a study combining the effectiveness of utilizing narrow-band ultraviolet light B therapy and etanercept for the treatment of psoriasis. The 12-week, wingle-arm, open-label study evaluated the combination of etanercept 50 mg twice weekly and NB-UVB thrice weekly in 86 patients. The primary outcome measure was > or =75% improvement from baseline in the Psoriasis Area and Severity Index (PASI 75). Other measures included PASI 90, PASI 100, and the Dermatology Life Quality Index (DLQI). At week 12, 26.0% achieved PASI 100, 58.1% achieved PASI 90, and 84.9% of patients achieved PASI 75. Mean improvement from baseline in DLQI was 84.4%. No unexpected, untoward adverse events were noted. It was concluded, "A 12-week course of etanercept plus NB-UVB phototherapy was well tolerated and produced clinically meaningful improvements in signs and symptoms of moderate to severe plaque psoriasis and in patient-reported outcomes."

In March 2012 Park et al[59] published on the effective treatment of etanercept and phototherapy-resistant psoriasis using the excimer laser. The case study reports on a patient who had a suboptimal response to etanercept monotherapy after 12 weeks of induction dosing (50 mg twice weekly) as well as to a combination of etanercept (50 mg once weekly-maintenance dosing) and narrowband ultraviolet B (NB-UVB) phototherapy three times weekly for an additional twelve weeks. Noticeable improvement was noted after the addition of NB-UVB and the patient's promising response to phototherapy influenced further management. Etanercept and NB-UVB were discontinued and the patient was initiated on excimer laser treatments twice weekly. After 4 weeks, the patient had a 75 percent reduction in Psoriasis Area Severity Index (PASI) score and after 7 weeks

had over 95 percent clearance of psoriasis. The authors propose that the excimer laser be considered in cases of biologic or conventional phototherapy failure in addition to being a standard treatment option or adjunct for the treatment of psoriasis.

In February 2015, Jang et al[75] investigated, in a 12 week open pilot study, the efficacy of a triple combination treatment, consisting of systemic corticosteroids, excimer laser, and topical tacrolimus, in patients with recently developed localized vitiligo. Fourteen patients (eight men, six women; mean age, 28.9 years) were enrolled in this study. Five patients had segmental vitiligo, whereas nine had focal vitiligo. All patients had recent-onset vitiligo lesions that had been evident for at least 6 months. The mean body surface area of the vitiligo was <3%. All patients were treated with low-dose oral prednisolone (0.3 mg/kg/day) for 4~8 weeks, 0.1% topical tacrolimus twice daily, and excimer laser twice a week for 12 weeks. The excimer laser was initiated at 100~200 mJ/cm^2, and the dose was increased by 50 mJ/cm^2. Among the 14 patients, repigmentation was scored as complete in five (35.7%), excellent in four (28.6%), good in one (7.1%), moderate in two (14.3%), and weak in two (14.3%) patients. Initial repigmentation was noted within 2 weeks in most of the patients. Among the five patients with complete repigmentation, two showed complete repigmentation within 1 month. The study concluded that the higher rate of 100% repigmentation compared to Sassi et al[49] (21.4%) were meaningful study results. The rapid onset of repigmentation of 1 month in two patients improved the patients' motivation and their compliance to therapy.

In July 2016 AbuHilal et al[58] evaluated the short term-efficacy and safety of apremilast in combination with at least one form of photo-, systemic, or biologic therapy in the treatment of chronic plaque psoriasis. A retrospective chart review was conducted for patients who received apremilast in addition to systemic, biologic, or phototherapy. A total of 81 patients were enrolled within subgroup combinations, apremilast was combined with narrow band-Ultraviolet B (NB-UVB) in 10 patients (15%), oral or subcutaneous methotrexate in 15 patients (22%), cyclosporin in 4 patients (6%), acitretin in 5 patients (7%), TNF inhibitors in 13 patients (19%; 7 infliximab, 4 etanercept, 2 adalimumab), both methotrexate and 1 of the TNF inhibitors in 7 patients (10%) (5 adalimumab and methotrexate, 2 infliximab and methotrexate), and combined with ustekinumab in 13 patients (19%). NBUVB with apremilast had the largest percentage of patients achieving PASI 75 at week 12, 89%, Ustekinumab-Apremilast has the closes at 85% and Methotrexate-Apremilast at 84%. Of those who completed at least 12 weeks of apremilast in combination with the other therapies, 17 patients (25%) developed diarrhea, and 16 patients (24%) developed nausea, weight loss was reported in 10 (15%) patients. One morbidly obese patient reported more than 25 lbs of unintentional weight loss. Four patients (6%) developed headaches, 2 patients (3%) developed transient acute urticarial rash not requiring discontinuation of medication (without other obvious underlying cause), and 2 patients (3%) developed nasopharyngitis and/or upper respiratory tract infection. No serious or life-threatening adverse effects occurred in any of the combination treatment subgroups.

In Novemebr 2017, Zhang et al published an RCT evaluating the use of the 308-nm targeted laser with and without Yiqiqubai granule for the treatment of vitiligo.24 Yiqiqubai granule is a therapy in traditional Chinese medicine, which is believed to activate blood circulation. The trial had 3 arms: 75 patients received twice- daily oral Yiqiqubai alone, 78 received weekly laser treatments alone, and 80 received both twice-daily oral Yiqiqubai and weekly laser treatments. All groups received treatment for 6 months. Two dermatologists not involved in the treatment assessed before and after pictures of the patients. Quality of life measures consisted of embarrassment, dress, social, and work components, measured on a 5-point scale. Following the 6 months of

treatment, the percentages of patients achieving 50% or more repigmentation were 43%, 47%, and 51% for the Yiqiqubai alone, laser alone, and combined Yiqiqubai and laser groups, respectively ($p<0.05$). While the quality of life improved in all 3 treatment arms, patients in the combined treatment arm reported significantly larger improvements than the arms receiving laser or Yiqiqubai alone.

VII. HIGH DOSE TREATMENT PROTOCOLS

In May 2000, Asawanonda et al[65] completed a dose-response study on the 308nm laser for the treatment of psoriasis. The excimer laser UVB radiation was given to each of 13 patients with at least 4 large, stable psoriasis plaques. Each plaque received 1,2,4, and 20 treatments. Within each plaque, 8 doses based on multiples of a predetermined minimal erythema dose (MED) were tested in distinct sites. The multiples were 0.5 and 1 (low dose); 2, 3, 4, and 6 (medium dose); and 8 and 16 (high dose). Treatment with high fluences produced significantly better results than that with medium and low fluencies at weeks 4, 6, 8, and 10 ($P<.05$). At 4 months' follow-up, all sites that received low or medium fluences had recurrences, whereas those that underwent a single treatment at 8 and 16 MED multiples remained in remission. The study concluded that with 308-nm UV-B radiation generated by an excimer laser, it is possible to clear psoriasis with as little as 1 treatment with moderately long remission. In contrast to traditional phototherapy techniques, this handheld excimer laser UV-B therapy is selectively directed toward lesional skin, thus sparing the surrounding normal skin from unnecessary radiation exposure. Treatment of other inflammatory diseases and limited psoriasis seems reasonable to pursue with this modality.

In May 2002, Trehan and Taylor[11] reported on a controlled clinical trial of 16 patients using a single high dose of 308nm light on psoriasis lesions. Although the single high-dose protocol produced significant blistering, they observed significant clearing (PASI 75) of psoriasis in 11 of 16 subjects. The duration of remission was 4 months for 5 patients, 2 months for 4 patients, and 1 month for 2 patients, and this was correlated to disease activity (stable plaques achieved longer remissions). No improvement was observed in the untreated control plaque areas. Statistical analysis determined the treatment to be effective over the 4-month follow-up period **($P<0.001$)**. Thicker plaques were observed to be less responsive to the single-dose protocol, leading to a subsequent study [14] using induration-based dosimetry.

In 2003 Tanghetti and Gillis[64] assessed the performance characteristics and clinical outcomes of psoriasis treatments using two technologically distinct sources of high-intensity, fiber-optically delivered therapeutic UVB. A pulsed, monochromatic 308 nm excimer laser and a continuous-wave, incoherent UVB light source were compared on ten psoriasis patients. Beam profile analyses and minimal erythema dose (MED) test spots revealed distinct energy distribution patterns from the two devices. Both systems cleared the treated psoriasis plaques equivalently, requiring no more than two to five weeks of high-dose treatments. The study concluded, when used at equally erythemogenic high doses, both systems produced rapid plaque clearance with minimal side effects. Unlike conventional phototherapy, localized UVB minimizes exposure to the healthy skin, making it suitable for patients with mild to moderate psoriasis, individuals with recalcitrant plaques, and for the successful treatment of lesions occurring on most body sites.

In 2012 Kagen et al[60] published on the clinical and biomarket effects of a single dose of TURBO laser UVB 308nm applied directly to psoriatic plaques. Eighteen patients with chronic plaque psoriasis received a single dose of 10 minimal erythema dose (MED) UVB and were followed for 8 weeks. Keratome and punch biopsies were assessed for T cell depletion and apoptosis following a single 308-nm dose of UVB. Patients demonstrated clinical improvement as indicated by decreased global Psoriasis Area and Severity Index scores and reduced numbers of pathogenic memory/effector T cells infiltrating lesional epidermis and dermis. Consistent with apoptosis induction, caspase activation increased in lesional T cells after treatment. The authors conclude that a single 10 MED dose of TURBO UVB is effective at reducing the severity and extent of psoriatic lesions and hypothesize that the reason a single treatment is sufficient to clear a psoriatic plaque is that the 10 MED dose is able to deliver sufficient photons to a microanatomic area of the lesion where susceptible pathogenic T cell mechanisms are operative.

In February 2014, Debbaneh et al evaluated Plaque-based sub-blistering dosimetry. Traditional dosimetry for excimer laser has been determined either through minimal erythema dose (MED) or a combination of the patient's Fitzpatrick skin type and the level of plaque induration. Authors developed "Plaque-based Sub-blistering Dosimtery" based on observations that administering anywhere from 8 to 16 multiples of MED to psoriatic plaques has resulted in clearance after one treatment with longer remission rates than the traditional dosing protocol. The authors describe a case in which a patient achieved PASI 75 following only two treatments with 308 nm excimer laser using this new protocol. Biopsies taken before and after treatment reveal a dramatic decrease in CD4 + T cells as well as TNF-alpha- and IL-2-producing T cells. This case demonstrates using a more aggressive dosing protocol determined by plaque testing is well-tolerated and can lead to excellent clearance with minimal side effects and comorbidity.

VIII. TAPERING TREATMENT PROTOCOLS

In 2004, Housman et al[67] evaluated the effectiveness of tapering the dose frequency on maintaining the clearance of psoriasis plaques after at least 75% clearance of a target plaque was achieved. The prospective case series was performed on 5 adults with stable, mild-to-moderate plaque-type psoriasis vulgaris. Patients received 308 nm UVB doses to affected areas. Initial dosing was based on multiples of a pre-determined minimal erythema dose (MED). Delivered fluences were 100, 150, 200, 250, 300 and 350 mJ/cm(2), corresponding to MED levels of 1 through 6. Subsequent doses were based on response to treatment. Induction treatments were scheduled biweekly for a total of 15 treatments. After improvement of disease, tapering began as follows: one treatment per week for 4 weeks, one treatment every other week for 4 weeks, and one final treatment 4 weeks later for a total of seven treatments. All patients achieved > or = 75% clearance of target plaques. No flares, i.e. 25% worsening of the percentage improvement, were noted upon completing the first month of the taper in any patient, either per percentage improvement or per PASI scores. One month after the second month of the taper (total of six treatments), no flares were noted and four out of five patients had no flares per PASI scores. No patients, either at the end of induction or at any interval during the taper, met the definition of a 50% rebound of PASI scores. Results reaffirm that biweekly UVB laser treatments promote clearance of psoriatic plaques. A tapering of laser treatments may be beneficial in maintaining the level of plaque clearance obtained from biweekly laser treatments.

IX. OTHER UTILITIES

In 2005 Obara et al [63] investigated the morphological changes of the rabbit tibia bone submitted to osteotomy with XeCl excimer laser. In this study, four tibias were irradiated with six different durations. The applied energy density was 6.7 J/cm(2) per pulse at a 4-Hz repetition rate. The 24 samples had similar and well-defined craters that were free of carbonization. The ablation rates per pulse, at 60-120 seconds, were 3.8 and 1.9 microm at the compact bone and the marrow tissue, respectively. The ablation process ceased after 120 sec, with a 1.6-mm crater depth. In this study, the laser used showed a self-limiting characteristic, which is a phenomenon that can be of great value in preserving important structures close to the working area, giving a margin of safety to the surgeon, in case of over-irradiation. This self-limiting effect is attributed to liquid filling the cavity by the bleeding and irrigation process.

In 2012 Beke et al[61] demonstrated high-resolution photocross-linking of biodegradable poly (propylene fumarate) (PPF) and diethyl fumarate (DEF) using UV excimer laser photocuring at 308 nm by modifying the curing depth in a micrometre range by adjusting the total energy dose (total fluence). The results presented here demonstrate that the proposed technique is an excellent tool for the fabrication of stiff and biocompatible structures on a micrometre scale with defined patterns of high resolution in all three spatial dimensions. Using UV laser photocuring at 308 nm will significantly improve the speed of rapid prototyping of biocompatible and biodegradable polymer scaffolds and enables its production in a few seconds, providing high lateral and horizontal resolution. This short timescale is indeed a tremendous asset that will enable a more efficient translation of technology to clinical applications. Preliminary cell tests proved that PPF : DEF scaffolds produced by excimer laser photocuring are biocompatible and, therefore, are promising candidates to be applied in tissue engineering and regenerative medicine.

X. TOXICITY

While the long-term safety profile and data on toxicity of the 308nm targeted NBUVB therapy is not fully established, the 311nm narrowband UVB technology has a larger safety profile. Narrowband UVB (311) nm phototherapy is a well-established, widely used and highly efficient treatment for psoriasis, but a big disadvantage is that large areas of unaffected skin are irradiated along with the psoriatic lesions. Because of this rational, Kollner conducted a study in 2005 comparing the safety and efficacy of the two technologies; Kollner concluded that the 308nm technology can clear patch psoriasis in a similar manner to standard phototherapy, with the advantage of the ability to treat exclusively the affected skin and with a reduced cumulative dose, thus perhaps reducing the long-term risk of carcinogenicity.

NB-UVB (308nm)

As excimer laser therapy is delivered directly to the affected areas by a handheld device with a spot size of 14 to 30 mm, adverse effects are limited to the area irradiated. Effects include erythema, burning, and hyperpigmentation.66,96 Blisters are noted more often with the use of higher fluences.65,66 The long-term safety of excimer laser therapy has not yet been fully established.

Pregnancy

Although the use of the excimer laser has not been studied in pregnant patients with psoriasis, its targeted nature suggests that the excimer laser is unlikely to have any teratogenic effects.[80]

Pediatric Use

Data regarding the use of the 308-nm excimer laser in children for psoriasis are limited but expert opinion is that it is safe.[81]

NB-UBV (311nm)

Burning with NB-UVB is generally comparable with that observed with BB-UVB exposure. Although NB-UVB is reported to be less phototoxic than BB-UVB in some studies,[89,90] other studies failed to show this discrepancy. [91,92] Although an unusual occurrence, lesional blistering has also been reported after exposure to NB-UVB.[93] However, because of the higher efficacy of NB-UVB, the total MED equivalent of UVB dose that occurs with NB-UVB treatment is far less than that occurs with BB-UVB, suggesting that the long-term risk of carcinogenesis may not be enhanced with NB-UVB.94 In fact, in a recent review of 3867 patients treated with NB-UVB in which the median number of treatments was 29 with 352 patients receiving more than 100 treatments, there was no significant association found with basal cell carcinoma, squamous cell carcinoma (SCC), or melanoma, with a median follow-up period of 5.5 years[95].

Pregnancy

Pregnancy is not a contraindication to the use of UVB therapy81 NB-UVB therapy has been used successfully in the treatment of psoriasis in pregnancy82-84 and should be considered first-line therapy in pregnant patients with plaque and guttate psoriasis who need a systemic approach to treatment. NBUVB therapy is unknown to have any teratogenic effects81.

Pediatric Use

In a retrospective review of 77 children treated with NB-UVB, of whom 35 had psoriasis, phototherapy was effective and well tolerated. Clearance was observed in 63% of patients with psoriasis. Erythema was the most common side effect. Anxiety was of significant concern in 5 patients, reactivation of herpes simplex occurred in two patients, and varicella occurred in one patient.85 Measures to make the phototherapy unit more child friendly have been suggested.86 Although there are no studies documenting the long-term safety of UVB phototherapy in childhood psoriasis, judicious use of this therapy as a second-line therapy in children whose disease fails topical therapy is reasonable for appropriately selected patients.

XI. CONCLUSION

Since the first study was conducted on the use of ultraviolet light to treat psoriasis in 1923 and the subsequent discovery of the optical wavelength dosage of 300-313nm in 1981 by Parrish, multiple studies have published on the safety and effectiveness profile of the 308nm laser for the treatment of psoriasis, vitiligo, atopic dermatitis and leukoderma. As such, the 308 nm excimer laser has emerged as a safe and effective treatment of the aforementioned diseases due to the targeted treatment modality of the laser.

Treatment of psoriasis commonly follows a step approach with topical therapy as first line, phototherapy as second line, and systemic medications reserved for when all other treatments fail. The 308 nanometer (nm) excimer laser has emerged as an important treatment option for patients with stable, localized mild-to-moderate

plaque psoriasis, especially for patients whose plaques are recalcitrant to topical therapy and is resultantly covered by virtually all insurance. The excimer laser offers numerous benefits to the patient, the physician, and third-party payor due to the effectiveness and efficiency of the targeted therapy.

Today, advances in the technology have enabled treatment of up to 20% BSA, a result of increasing the laser repetition rate and allowing quicker patient treatments. High Dose Treatment Protocols continue to increase the efficiency of patient treatment and combination therapy has demonstrated ways to increase the effectiveness of traditional monotherapies.

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XIII. SPREADSHEET OF CLINICAL TRIALS

Table 1. Psoraisis

Ref.	Indication	Publ. Date	Authors	N (patients) N=958	Result	Statistical Significance
[5]	Psoriasis	11/97	Bonis et al	10	*"The number of treatments up to complete clearance with the 311 nm narrowband UVB light was 29-33 (mean 30.1) while that with the 308nm XeCl [excimer] laser was 8-10 (mean 8.33)."*	[N/A]
[6]	Psoriasis	5/02	Novak et al	21	*"The mean number of treatments [to complete clearance] was 9.2"*	P<0.05
[11]	Psoriasis	5/02	Trehan et al	16	*[Of 16 subjects, high dose protocol] "Eleven showed significant improvement within 1 month, and 5 still demonstrated persistent areas of clearing at 4 months"*	P<0.001
[12]	Psoriasis	6/02	Feldman et al	92	*"72% (66/92) achieved at least 75% clearing in an average of 6.2 treatments.* *84% of patients (95% confidence interval [CI], 79%-87%) reached improvement of 75% or better after 10 or fewer treatments."*	95% conf. interval using Kaplan-Meier method
[13]	Psoriasis	11/02	Trehan et al	15	*"The mean number of treatments to achieve >95% clearance was 10.6, . . and the mean remission time was 3.5 months. "Improvement in posttreatment PASI scores was statistically significant at 4, 8, and 16 weeks (P<.01)"*	P<0.01
[14]	Psoriasis	6/03	Taneja et al	14	*"Compared with controls, treated plaques showed significant improvement (P<0.001)"* *"The mean modified PASI scores of the treated plaques improved steadily as treatment progressed: from 6.2 (control, 6.4) before treatment; to 2.6 (control, 6.2) after treatment 5; to 1.2 (control, 6.9) after treatment 10; to 1.0 (control 7.0) after treatment 13."*	P<0.001
[15]	Psoriasis	7/03	Fikrle et al	28	*"Most patients showed clear improvement. In 90% the PSI at the end of* *treatment was reduced by at least 50%; in 72% it was only 33% of the pre- treatment value. . . In 6 patients, the psoriatic lesion was still absent after 1 year, while in an additional 7, there had been long term improvement. . . The use of the 308nm excimer laser is effective for chronic localized psoriasis and may lead to long-lasting remissions."*	[N/A]
[16]	Psoriasis	12/03	Gerber et al	142	*"[Of patients in the standard protocol,] 65.7% (67 of 102) achieved a >=90% clearance after 10 or less treatments; 87 of 102 patients (85.3%) achieved a >=90% or complete clearance after 13 treatments [or less; median 10.8 treatments]. . . We found the same clearance rate [with the induration protocol], as in the large group, of 83.7% (34 of 40). However, in contrast, this result was reached in 7.07 +/- 2.15 sessions. . . Excimer laser- generated 308-nm UVB radiation is one of the most effective treatment forms for moderate and chronic forms of psoriasis. . . UVB laser treatment for localized psoriasis has considerable advantages over current topical and conventional UVB treatment. We observed a faster clearance rate at less exposure and a greater risk-benefit ratio as there is less risk for uninvolved skin. . . Furthermore, the study has shown the excimer laser to be effective in treating thick, scaled plaques on the knees and elbows, which are often resistant to any conventional treatment."*	P<0.05
[17]	Psoriasis	3/05	Pahlajani et al	16	*"The children's group exhibited a greater reduction (p=0.008) from mean baseline target PSS score [91.3% reduction in 12.5 Tx] as compared to the adult treatment group [61.6% reduction in 9.7 Tx]. . . In conclusion, the 308nm excimer laser appears to be a safe and effective treatment for* *localized psoriasis in children as well as in adults."*	P=0.02
[18]	Psoriasis	8/06	Morison et al	35	*"All patients improved. 17/35 (49%) of patients cleared>95% (mean: 21 treatment; range: 6-52) and 16/35 (45%) cleared 50-95%. . . The excimer laser is a successful approach to treatment of psoriasis of the*	[N/A]

					scalp being a simple treatment that can be performed in a short period of time and which has a high rate of effectiveness."	
[27]	Psoriasis	11/05	Taibjee et al.	15	*"Mean improvement in PSI was 4.7 with excimer and 2.7 with PDL. PSI improvement was significantly greater with excimer than PDL (P=0.03) or both control plaques (P < 0.001). Clinical response to treatment was significantly greater for excimer than PDL (P = 0.003) or both controls (P < 0.001). The study concluded that excimer appeared on average more efficacious"*	P=0.03 P<0.001
[29]	Psoriasis	6/06	Rivard et al.	28	*"Over 80% has greater than 87% improvement after an average of 12 treatments."*	[N/A]
[37]	Psoriasis	1/10	Gattu	12	*"Of the 12 patients who completed the treatment phase, 54% achieved PASI 75. During the 6-month follow-up period 83% maintained PASI 50 with no treatment. The study concluded the laser is an effective treatment with a favorable remission rate."*	[N/A]
[18]	Psoriasis (Scalp)	8/06	Morison et al	35	*"All patients improved. Seventeen/35 (49%) of patients cleared>95% (mean: 21 treatments; range: 6-52) and 16/35 (45%) cleared 50-95%"*	[N/A]
[79]	Psoriasis (Scalp)	7/14	Al-Mutairi et al	26	*"Twenty-two of the 23 patients with scalp psoriasis showed improvement, while one patient showed no change; The percentage improvement from baseline in PSSI score was 78.57 %.*	[N/A]
[79]	Psoriasis (palmoplantar)	7/14	Al-Mutairi et al	15	*"The mean number of treatments to achieve clearance (equal to 90 % reduction of PSI score) was 16. Two patients relapsed at the end of 6 months after the therapy. Investigators concluded the 308-nm excimer laser is an effective, safe, easy, and relatively quicker method for the treatment of psoriasis at difficult to treat sites, with good results in a somewhat short time.*	[N/A]
[28]	Psoriasis (palmoplantar)	5/06	Nistico et al.	54	*"After 4 months of treatment we observed a complete remission in 31 patients, a partial remission in 13 patients, and a moderate improvement in 10 patients. The study concluded that the excimer laser is an effective treatment for selected forms of PP."*	[N/A]
[34]	Psoriasis (palmoplantar)	10/08	Han et al	15	*"[patients] showed a 52.5% improvement in the mean severity index score after a total of 25 MEL treatments (1 x /week) with only one patient (6.7%) achieving clearance… concluding the therapy as safe and effective treatment modality for patients with palmoplantar psoriasis"*	[N/A]
[33]	Psoriasis (vulgaris)	12/07	He YL et al	40	*"After a total of 15 treatments, (1) the Psoriasis Area and Severity Index score was improved by 90.19+/-10.12% and 77.34+/-17.04% in macular type and chronic plaque type, respectively (P<0.05) and (2) the average treatment sessions were 13.7 times. The study concluded the 308nm excimer laser is safe and effective for the treatment of psoriasis vulgaris"*	P<0.05
[34]	Psoriasis (vulgaris)	10/08	Han et al	30	*"patients with psoriasis vulgaris showed a 74.6% improvement in the mean psoriasis area and severity index score after a total of 16 MEL treatments (2 x /week) with 36.7% of the patients (n=11) achieving clearance…. concluding the therapy as safe and effective treatment modality for patients with mild-to-moderate psoriasis vulgaris"*	[N/A]
[56]	Psoriasis	3/11	Rogalski et al	54	***[Combination therapy: evaluates response of topical only, laser only and combination therapy with topical medication and laser]…*** *"The combined therapies resulted in 23 cases of partial clearance in both treatment arms…The average reduction of modified PASI scores was higher in combination than in topical treatment alone (49.8% calcipotriol + excimer versus 22.9% calcipotriol, 49.7% dithranol + excimer versus 26.8% dithranol). After six months there was a total clearance of 30.5% dithranol + excimer. The results concluded that the treatment of plaque-type psoriasis with laser in combination with topical treatment is a safe and effective therapy. The best long-term results can be obtained by the application of dithranol and excimer laser.*	[N/A]

[50]	Psoriasis (vulgaris)	6/12	Dong et al	40	*[C**ombination therapy**: **flumetasone ointment with excimer laser therapy vs excimer laser monotherapy]**…20 patients treated with combination therapy, 20 patients treated with monotherapy..” the psoriasis area and severity index score was improved by 82.51 ± 11.24% (combination group) and 72.01 ± 20.94% (laser group) respectively (P > 0.05)… The clinical data suggest that combination treatment using flumetasone ointment and a 308-nm “*	P>0.05
[57]	Psoriasis	8/12	Wong et al	2	*[**Combination therapy: case series on excimer laser, clobetasol spray and calcitriol ointment**]… Patient 1 started with PASI 14.6 and reached PASI 75 in 10 treatments. After 12 treatments, PASI 1.9 was achieved. The second patient started treatment at PASI 9.6 and reached PASI 75 after 10 treatments; sixteen treatments were needed to achieve PASI 1.8*	[N/A]
[77]	Psoriasis (vulagris)	8/14	Tang et al	32	*[**Combination therapy**: **calcipotriene ointment in combination with excimer laser vs excimer laser monotherapy**]… “Effective rate on week 6 in control group [laser monotherapy] (56.25%) was lower than treatment group [combination therapy] (84.37%) (P < 0.05). The two groups showed that PASI scores on weeks 2 and 4 after treatment were significantly lower than before treatments (P < 0.05), and PASI scores on week 6 in treatment group was significantly lower than control group (P < 0.05). The study concluded that the treatment of psoriasis vulgaris with 308 nm excimer laser in combination with external application of calcipotriene ointment can improve long-term treatment efficacy, decrease cumulative laser doses, and reduce adverse effects induced by laser irradiations.”*	P<0.05
[53]	Psoriasis	6/16	Levin et al	30	*[C**ombination therapy: combination clobetasol spray and calcitriol ointment and excimer laser]**… 83% of patients (25/30) achieved PASI-75 [65-94%, 95% confidence interval (CI)] at week 12, average of 10.3 laser treatments. For PGA, there was an estimated decrease of 3.6 points (3.1-4.1, 95% CI, p < 0.0005) by week 12. In conclusion, the combination of excimer laser with alternating clobetasol and calcitriol application has shown to be a promising combination of therapies for the treatment of moderate to severe generalized psoriasis.”*	P<0.005
[58]	Psoriasis	7/16	AbuHilal et al	81	*[Retrospective Chart Review] **[Combination therapy: apremilast in combination with one form of photo-,systemic, or biologic therapy]**… NBUVB with apremilast had the largest percentage of patients achieving PASI 75 at week 12, 89%, Ustekinumab-Apremilast has the closes at 85% and Methotrexate-Apremilast at 84%.*	[N/A]
[59]	Psoriasis	3/15	Park et al	Case Report	***[Combination therapy: etanercept and excimer]** Etanercept was initiated at the induction dose of 50 mg subcutaneously twice weekly. Minimal improvement was observed at week 4 and week 8 visits, and the patient had a mild flare of disease by week 12. NB-UVB was introducted, resulting in a 35% reduction in disease severity by week 16. Results maintained through 6 months. Etanercept had 3 week wash out period and started with EXTRAC twice weekly including clobetasol spray and calcitriol ointment in alternating two week intervals. Pateint reached PASI 75 at week 4 of excimer treatment.and PASI 95 at week 7, complete clearance at 10.5 weeks. The authors conclude, “We propose that the excimer laser may be useful in resistant psoriasis and considered an option as first-line therapy or after treatment failure”*	[N/A]
[66]	Psoriasis	7/06	Koo et al		***[Combination Therapy: Alefacept and UVB}** Twenty-four patients received alefacept in combination with UVB in course A, 21 in course B and 24 in course C. A patient was not required to maintain the same course of concomitant therapy for all three treatments. Results of the cohort analysis suggest that the combination of alefacept and UVB phototherapy is an effective treatment for chronic plaque psoriasis, with a majority of evaluated patients in each course of therapy experience 2 or more categories of PGA improvement from their course A baseline. The results of UVB cohort were better than those of other cohorts in the study, including alefacept monotherapy and alefacept in combination with retinoids or topical steroids.*	[N/A]

[99]	Psoriasis	6/08	Gisondi et al	60	***[Combination Therapy: Etanercept and acitretin}*** *Sixty adult patients with moderate to severe chronicplaque psoriasis were randomized into three groups to receive etanercept 25 mg twice weekly subcutaneously, oral acitretin 0.4 mg kg(-1) daily or etanercept 25 mg once weekly plus acitretin 0.4 mg kg(-1) daily. t week 24, PASI 75 response was achieved by 10 of 22 patients in the etanercept group (45%), six of 20 in the acitretin group (30%) and eight of 18 (44%) in the group treated with etanercept plus acitretin (P = 0.001 for both etanercept groups compared with acitretin alone). A 50% or greater improvement from baseline in PASI was achieved by 15 of 22 (68%), 10 of 20 (50%) and 12 of 18 (67%) patients, respectively (P = 0.001). The safety profiles of the three groups were similar*	P=0.001
[100]	Psoriasis	3/08	Kircik et al	86	***[Combination Therapy:Etanercept and NB-UVB for treatment of psoriasis]*** *This 12-week, single-arm, open-label study evaluated the combination of etanercept 50 mg twice weekly and NB-UVB thrice weekly. At week 12, 26.0% achieved PASI 100, 58.1% achieved PASI 90, and 84.9% of patients achieved PASI 75. Mean improvement from baseline in DLQI was 84.4%. It was concluded, "etanercept plus NB-UVB phototherapy was well tolerated and produced clinically meaningful improvements in signs and symptoms of moderate to severe plaque psoriasis and in patient-reported outcomes."*	[N/A]

Table 2. Vitiligo

Ref.	Indication	Publ. Date	Authors	N (patients) N=907	Result	Statistical Significance
[68]	Vitiligo	4/04	Choi et al.	69	*"The rate of repigmentation continued to increase with the number of treatments up to 20 sessions, and then showed plateaus between 20-30 sessions."*	[N/A]
[74]	Vitiligo	1/15	Al-Shobaili	134	*"Excimer laser treatment significantly improved quality of life in vitiligo patients, with improvement observed in five of six DLQI domains. Treatment-induced changes in the VAS score showed a significant decline in life disturbance and improvement in life satisfaction… Patients with multiple focal lesions should be treated by excimer laser even if some lesions may not show significant clinical improvement"*	[N/A]
[42]	Vitiligo (nonsegmental)	6/10	Le Duff et al	20	*"[excimer lamp vs excimer laser] The treatment results for efficacy of repigmentation of at least 50% (P=0.006); however the lamp induced more erythema than the laser. Both methods were safe and effective."*	P=0.006
[52]	Vitiligo (nonsegmental)	11/15	Latif et al.	44	*[excimer compared to topical combination of calcitriol and betamethasone] … There was a significant difference between both groups regarding the onset of repigmentation (p-value < 0.05), whereas group B [excimer] showed early sign of repigmentation in first 4 weeks of treatment in 16 patients versus 7 patients in group A [topical combination].*	[N/A]
[45]	Vitiligo	9/04	Passeron et al	43	***[Combination therapy: tacrolimus combination laser therapy vs laser monotherapy]…."*** *Repigmentation was observed in all patients in group A [combination therapy] and in 85% of group B lesions [laser therapy only]. Repigmentation was not observed in the untreated control group. A repigmentation rate of 75% or more was obtained in 70% of the Group A lesions and 20% of the group B lesions. The mean number of sessions necessary for an improvement of repigmentation was 10 in group A and 12 in group B. The study demonstrated the combination treatment of 0.1% tacrolimus ointment plus the 308-nm excimer laser is superior to 308-nm excimer laser monotherapy for the treatment of UV-resistant vitiliginous lesions (P<.002)."*	P<0.002
[46]	Vitiligo	2/04	Kawalek et al	8	***[Combination therapy: tacrolimus combination laser therapy vs laser monotherapy]…."*** *Fifty percent of patches treated with combination therapy achieved 75% repigmentation compared with 20% for the placebo group, i.e. laser alone. Subjects who responded successfully repigmented faster (19%) with combination therapy compared with the excimer alone… The study demonstrated that combining topical immunomodulators with known phototherapeutic modalities may represent a key advancement in the treatment of the disease. "*	[N/A]
[49]	Vitiligo	10/08	Sassi et al	76	***[Combination therapy: topical hydrocortisone 17-butyrate cream combination laser therapy vs laser monotherapy]****… seven [16.6%; 95% confidence interval (CI) 5.3-27.8%] patients in the excimer monotherapy arm and 18 (42.8%; 95% CI 27.8-57.8%) in the combination arm showed > or = 75% reduction of vitiligo lesions at 12 weeks (chi(2) test 6.89, P = 0.0087). Clearance was observed in two (4.7%; 95% CI 1.6-11.2%) and nine (21.4%; 95% CI 9.0-33.8%) patients, respectively (Fisher's exact test P = 0.04). It was concluded that Recalcitrant vitiligo of the face and neck may benefit from the combination of excimer laser phototherapy with topical hydrocortisone 17-butyrate cream."*	P = 0.0087 P=0.04

[47]	Vitiligo	10/10	Asawanonda et al	10	***[Combination therapy: excimer laser plus topical tetrahydrocurcuminoid vs laser monotherapy]****… The study outcomes showed statistically significant repigmentation in both groups. The overall degree of repigmentation was slightly better in the combination group at 8 and 12 weeks (p = 0.078 and 0.158).*	P= 0.078 P= 0.158
[54]	Vitiligo (facial)	6/11	Mouzakis et al	3	***[Combination therapy: excimer laser in conjunction with topical calcipotriene]****… Two patients achieved greater than 75% repigmentation after 22 treatments or less (11 weeks) and one patient achieved 75% repigmentation after 40 treatments (20 weeks).*	[N/A]
[78]	Vitiligo	10/14	Matin et al	150	***[Combination therapy: combination excimer laser and 0.01% tacrolimus vs excimer laser monotherapy in Iranian population]****… The higher efficiency of the combination therapy on repigmentation was statistically significant (P = 0.006).*	P=0.006
[55]	Vitiligo	11/15	Namazi et al.	30	***[Combination therapy: topical ethyl vanillate in combination with excimer laser therapy]****… Result showed 36.6% of lesions which were treated with ethyl vanillate showed a change in pigmentation (mostly mild clinically) compared with 13.3% in placebo side. The study concluded ethyl vanillate may serve as an adjunct therapy for the treatment of vitiligo, although changes in pigmentation are mild clinically."*	[N/A]
[72]	Vitiligo	1/16	Solimoan et al	30	***[Combination therapy: combination topical antioxidant hydrogel and excimer laser vs excimer laser monotherapy]****… Group A [combination therapy] lesions showed significantly greater efficacy than group B [monotherapy] (p < 0.001), especially on treating UV-sensitive lesions with no side effects."*	[N/A]
[70]	Vitiligo (nonsegmental)	4/16	Park et al	276	***[Combination therapy: excimer laser monotherapy vs tacrolimus ointment vs combination excimer laser and tacrolimus ointment]****… the combination of tacrolimus plus excimer laser was significantly more effective than either tacrolimus or excimer laser alone (P < 0.001 and P < 0.01, respectively) for the first 6 months. However, this superiority was not observed after the initial 6 months of treatment. In vitro, the combination of tacrolimus plus excimer laser led to a higher level of melanogenesis than with either treatment alone. A combination treatment with topical tacrolimus and an excimer laser may be useful as an induction therapy for up to 6 months, but continuation of this therapy for > 6 months might not provide a better final outcome than monotherapy."*	P<0.01
[75]	Vitiligo (segmental and localized)	2/15	Jang et al	14	***[Combination Therapy: triple combination treatment of systemic corticosteroids, excimer laser and topical tacrolimus]****…repigmentation was scored as complete in five (35.7%), excellent in four (28.6%), good in one (7.1%), moderate in two (14.3%), and weak in two (14.3%) patients. Initial repigmentation was noted within 2 weeks in most of the patients.*	[N/A]

Table 3. Other Skin Diseases

Ref.	Indication	Publ. Date	Authors	N (patients) N=160	Result	Statistical Significance
[30]	Atopic Dermatitis	6/06	Baltás et al	15	*"After 1 month of laser therapy, the clinical scores were significantly lower than the initial values. Similar decreases were observed for the quality of life and pruritus scores. No serious or unpleasant side-effects were observed, suggesting that the xenon chloride excimer laser is an effective and well-tolerated treatment for localized atopic dermatitis."*	[N/A]
[36]	Atopic Dermatitis	11/09	Wollenschlager	57	*"Complete remission was achieved in nearly 85% of the patients and partial remission was achieved in 15% of the patients after 10 treatments. It was determined that excimer UVB treatment expands the therapeutic options in patients with localized and therapy-resistant atopic dermatitis enormously."*	[N/A]
[48]	Atopic Dermatitis (Purigo Form)	5/10	Brenninkmeijer	13	*"A significant improvement of mean PAIS was seen for the laser and [clobetasol propionate] CP at week 10 compared with baseline: 9.2 ($P < 0.01$) improvement for the laser treated areas and 8.0 ($P < 0.01$) for the CP treated areas. During follow up the excimer showed more improvement compared with CP and histological evaluation showed marked decrease of epidermal thickness and inflammatory infiltrate at the laser treated sites"*	P<0.01
[43]	Mycosis fungoides (MF)	3/07	Passeron et al.	10	*"Eighty-six percent of patch-stage or plaque lesions had completely cleared up by the end of treatment and 14% had cleared up partially, with a global response rate of 100%. The mean number of sessions was 15 (6 to 46 sessions) corresponding to a mean treatment duration of 2 months. Persistent complete clearance was observed in 13 of 19 (68%) lesions. Histologically, the lesion showed healing where it had disappeared, except for one case with a few mycosis cells in the epidermis despite a clinical appearance of healing. The study demonstrated efficacy of the laser for mycosis fungoides*	[N/A]
[44]	Mycosis fungoides (MF)	10/04	Passeron et al.	5	*"Treatment was administered twice weekly until >90 improvement was achieved. A clinical response was obtained for 4 out of the 5 patients and minimal residual activity was observed in the fifth patient. Clinical healing was obtained in 11 of 21 sessions (average 15 sessions)."*	[N/A]
[41]	Palmoplantar pustulosis	6/11	Furuhashi et al	20	*"At baseline, the mean (±SD) PPPASI score was 19.5 (±8.1) and it decreased steadily throughout the treatment period: 13.2 (±6.6) at 10 treatments, 10.9 (±9.6) at 20 treatments and 9.5 (±8.9) at 30 treatments. The PPPASI score was significantly lower after 20 treatments than at baseline ($P < 0.05$) and even lower after 30 treatments ($P < 0.01$)"*	P<0.01
[73]	Alopecia areata	6/15	Byun et al	10	*"Photographic assessments by both dermatologists and individuals of the general population showed objective improvements after excimer laser therapy… The conclusion was that the 308-nm excimer laser has a therapeutic effect on AA, which is proven by photograph and phototrichogram analysis by a side-by-side comparison"*	[N/A]
[69]	Eczema (chronic hand and foot "CHFE")	8/16	Shroff et al	30	*[retrospective chart review]…" Improvements in clinical scores included a 69% reduction in average physician's global assessment (PGA) scores (from 2.77 at baseline to 0.87 after treatment, $P < 0.0001$) with a parallel reduction in average modified total lesion/symptom scores of 70% (from 10.2 to 3.1, $P < 0.0001$). The study concluded that the excimer laser shows excellent and sustained efficacy for the treatment of CHFE."*	P<0.0001

XIV. DATA SUMMARY OF COMBINATION THERAPY FOR PSORIASIS

Chart 1. Combination Therapy for Psoriasis[77,50,56]

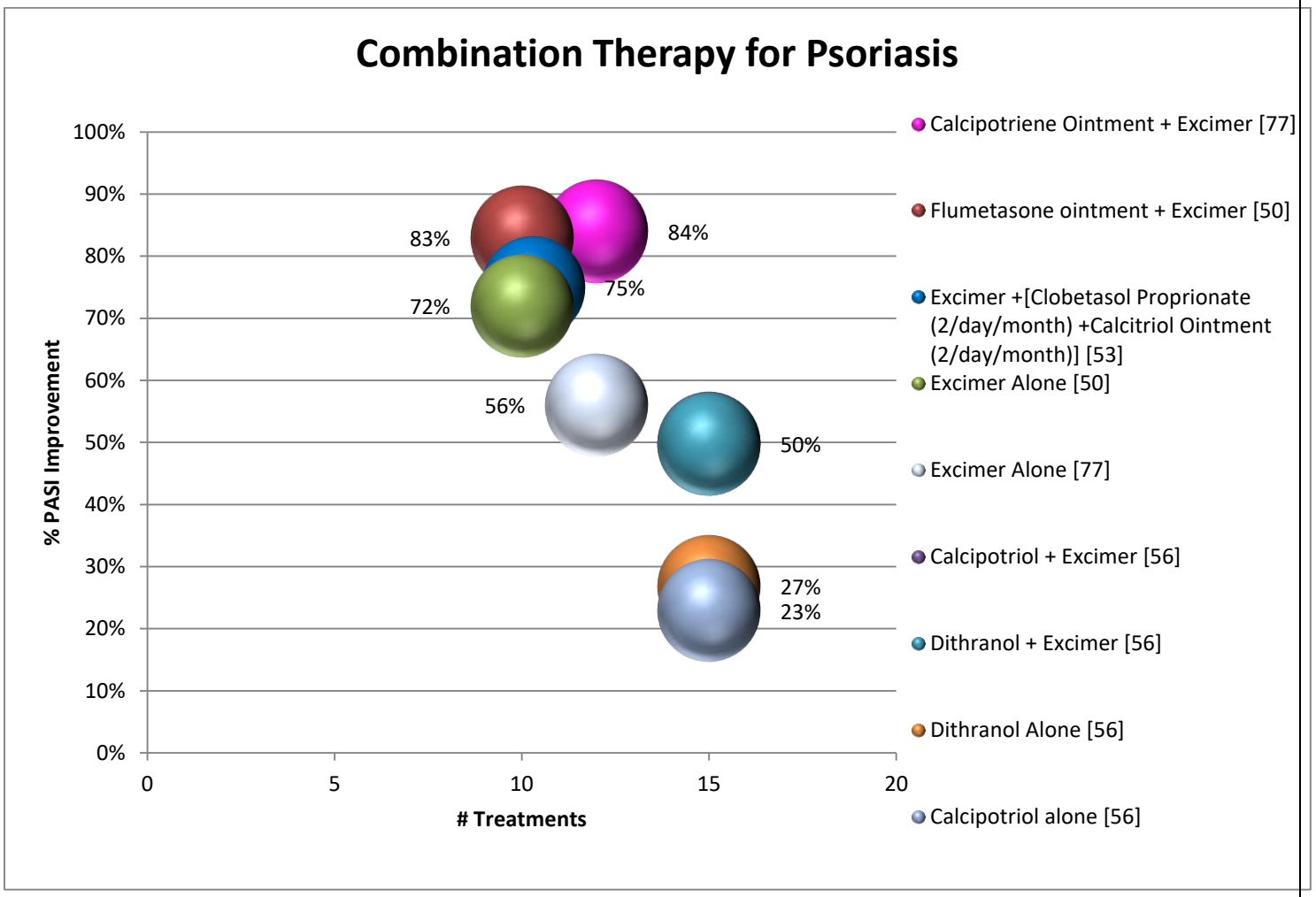

Chart 1 presents three studies which evaluate the excimer laser in combination with topicals or as monotherapies for the treatment of psoriasis. A study by Tang et al[77] compares calcipotriene ointment in combination with excimer therapy to excimer alone, Dong et al[50] compares flumetasone ointment with excimer laser therapy versus excimer laser monotherapy and Rogalski et al[56] compares calcipotriol and excimer versus calcipotriol alone as well as dithranol and excimer versus dithranol alone. Best results were observed with the combination of calcipotriene ointment and excimer laser with 84% improvement in PASI scores compared to baseline.

Chart 2. Amremilast + Other Therapeutic for Psoriasis[58]

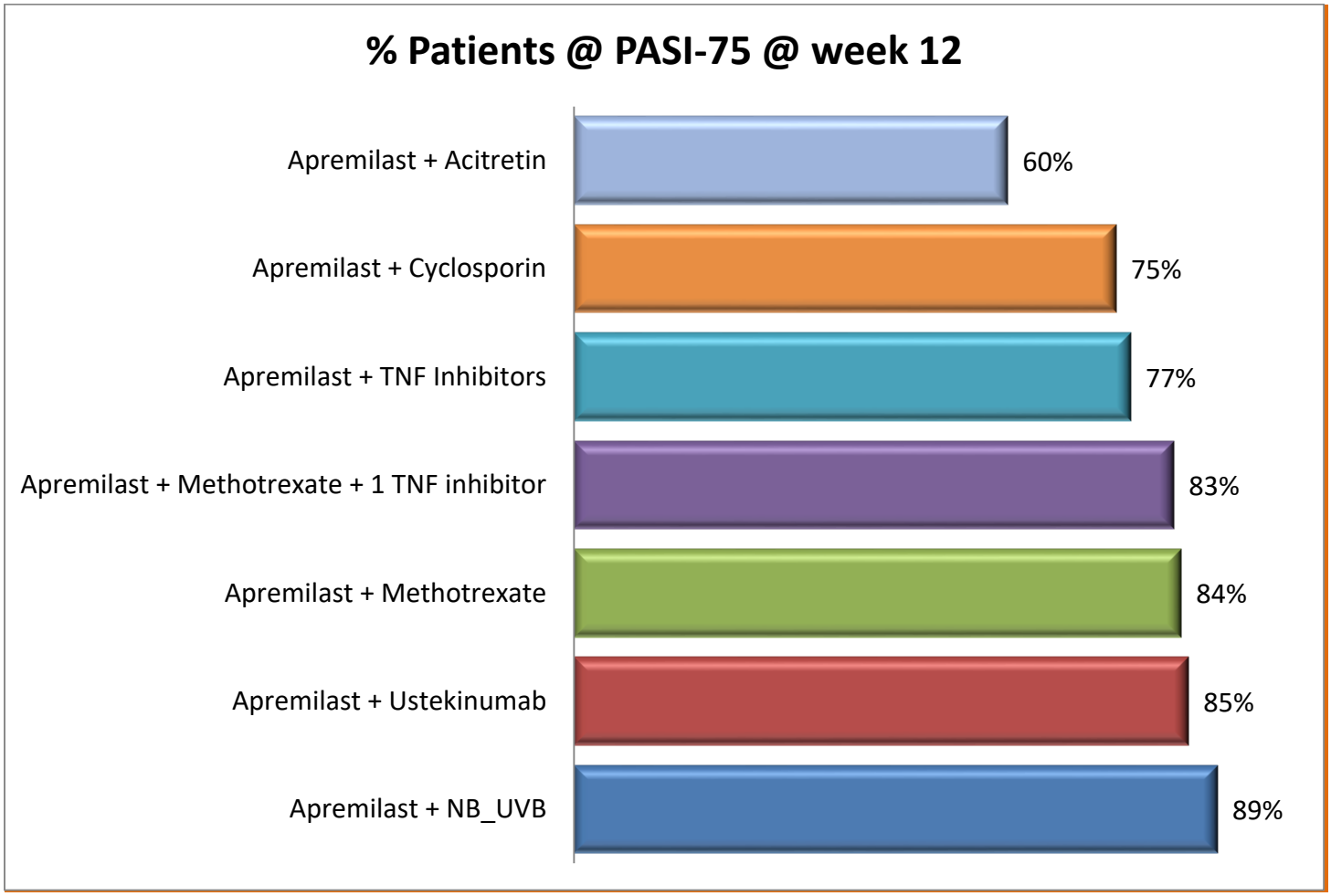

Chart 2 presents a study by AbuHilal et al[58] that evaluates the short-term efficacy of apremilast in combination with at least one form of photo-, systemic, or biologic therapy in the treatment of chronic plaque psoriasis. Apremilast and narrowband UVB (excimer) had the largest percentage of patients, 89%, reaching PASI-75 at week 12.

Note: Of those who completed at least 12 weeks of apremilast in combination with the other therapies, 17 patients (25%) developed diarrhea, and 16 patients (24%) developed nausea, weight loss was reported in 10 (15%) patients. One morbidly obese patient reported more than 25 lbs of unintentional weight loss. Four patients (6%) developed headaches, 2 patients (3%) developed transient acute urticarial rash not requiring discontinuation of medication (without other obvious underlying cause), and 2 patients (3%) developed nasopharyngitis and/or upper respiratory tract infection. No serious or life-threatening adverse effects occurred in any of the combination treatment subgroups.

Chart 3. Combining Etanercept and Acitrein in Therapy of Psoriasis[99]

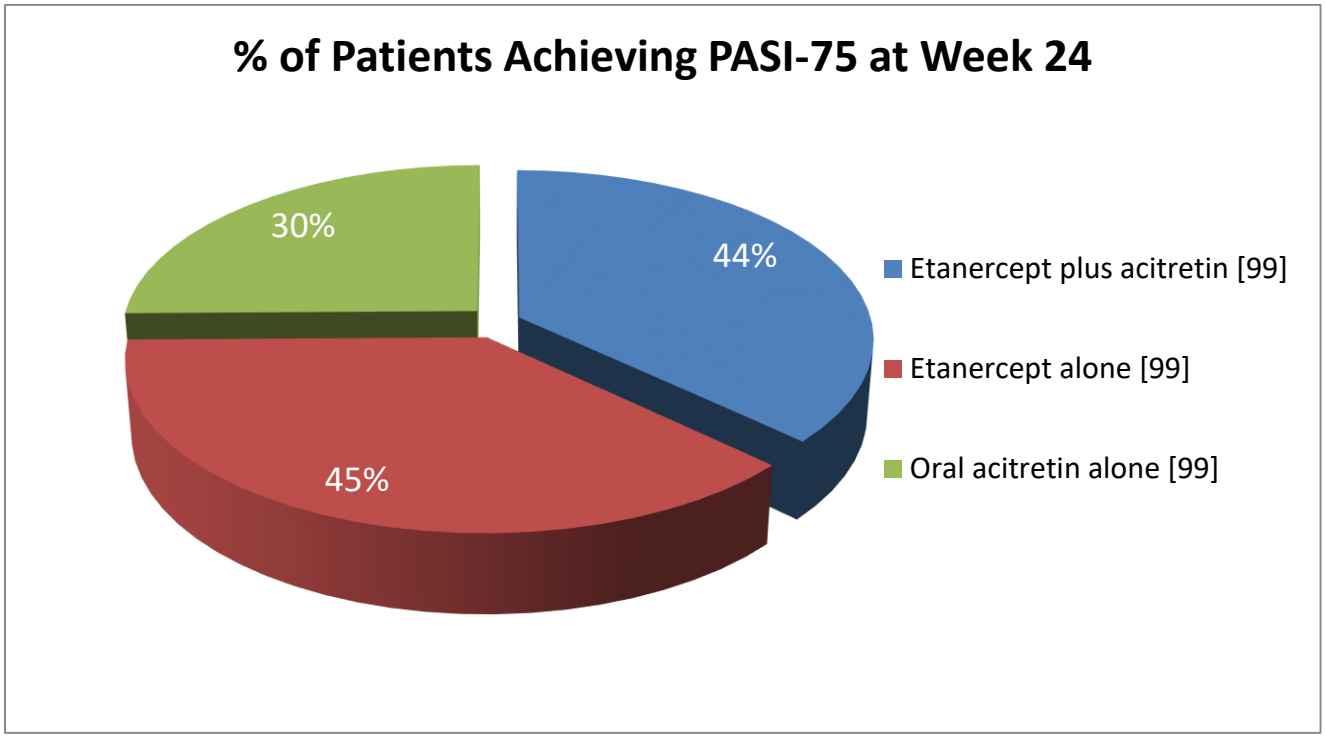

Chart 3 presents a study by Gisondi et al[99] that evaluated the combination of biologics with conventional agents for psoriasis. The team conducted a 24-week, randomized, controlled pilot study with 60 patients. Each patient was randomized into one of 3 groups to receive etanercept 25 mg twice weekly subcutaneously, oral acitretin 0·4 mg kg−1 daily or etanercept 25 mg once weekly plus acitretin 0·4 mg kg−1 daily. At week 24, PASI 75 response was achieved by 10 of 22 patients in the etanercept group (45%), six of 20 in the acitretin group (30%) and eight of 18 (44%) in the group treated with etanercept plus acitretin (P = 0·001 for both etanercept groups compared with acitretin alone). A 50% or greater improvement from baseline in PASI was achieved by 15 of 22 (68%), 10 of 20 (50%) and 12 of 18 (67%) patients, respectively (P = 0·001). The safety profiles of the three groups were similar.

Chart 4. Combining Etanercept and NB-UVB for Psoriasis[100]

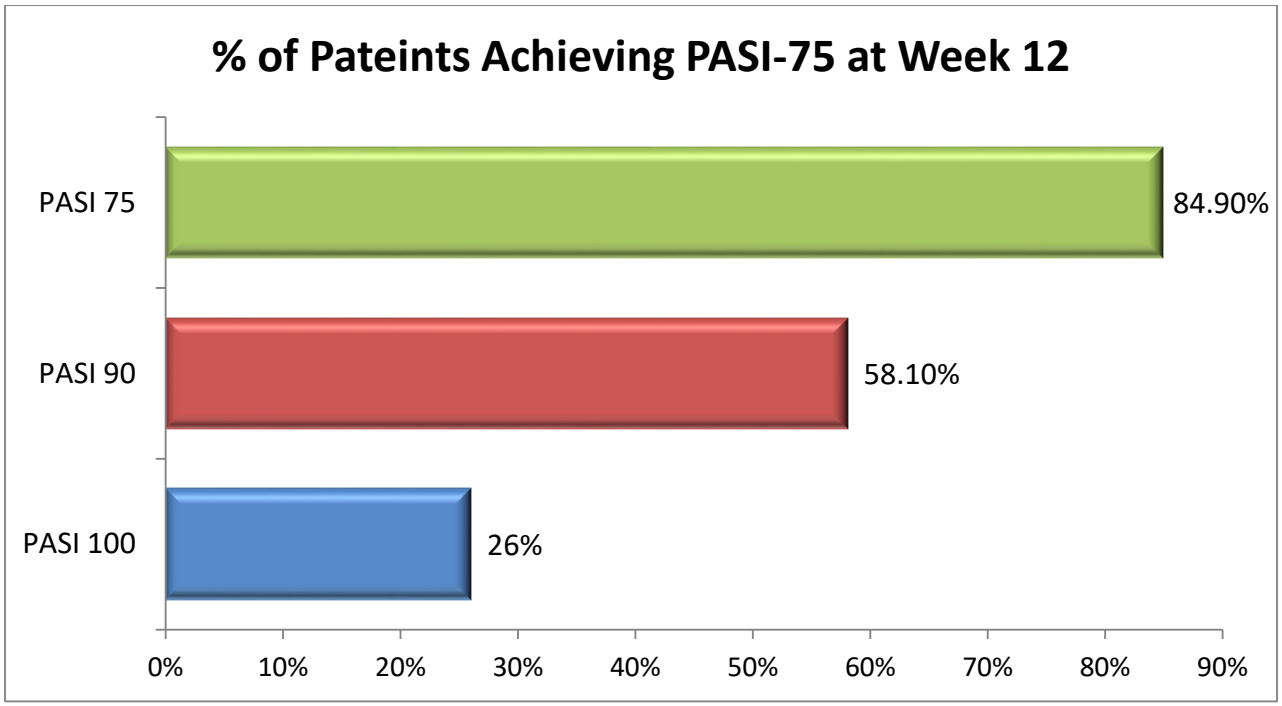

Chart 4 reports on a 12-week study by Kircik et al[100] of 86 patients combining NB-UVB and etanercept for the treatment of moderate to severe plaque psoriasis. The 12-week, single-arm, open-label study evaluated combination of etanercept 50 mg twice weekly and NB-UVB thrice weekly in 86 patients. At week 12, 26.0% achieved PASI 100, 58.1% achieved PASI 90, and 84.9% of patients achieved PASI 75. These study results appear to trump the results in Chart 3 presenting PASI-75 achieved in a smaller portion of patients over 24-weeks. In combination, these study results suggest the use of etanercept with NB-UVB is more clinically meaningful than the use of etanercept alone, oral acitretin alone or etanercept plus acitretin for the treatment of plaque psoriasis.

SECTION II: CURRENT PROCEDURAL TERMINOLOGY (CPT) CODING

CPT CODES: 308nm EXCIMER LASER

Table 4. CPT Codes for Excimer Laser Treatment

CPT Code	Description
96920	Laser treatment for inflammatory skin disease; total area less
96921	250 sq cm to 500 sq cm
96922	over 500 sq cm

Note: While the above CPT codes are not specific to the excimer laser for the treatment of inflammatory skin diseases, many insurance companies that have adopted payment policies have specified that these codes are valid only for the excimer laser, thereby eliminating confusion with other, less proven types of laser systems.

SECTION III: Appendices

A. Wirtzer Letter [The American Academy of Dermatology's (AAD) representative to the AMA CPT Advisory Committee]
B. National Psoriasis Foundation (NPF) Statement

C. Lebwohl Letter [Chairman of the Psoriasis Task Force of the AAD]
D. American Society for Dermatologic Surgery Statement
E. Florida Medicare Part B Medical Policy
F. South Carolina Medicare Part B Medical Policy
G. Empire Medicare Services (Downstate NY and NJ) Medicare Medical Policy
H. GHI NY (Queens County) Medicare Part B Medical Policy
I. BlueCross Blue Shield of Alabama Medical Policy
J. Arkansas BlueCross BlueShield Medical Policy
K. CareFirst BlueCross BlueShield Medical Policy
L. Wellmark BlueCross BlueShield of Iowa/South Dakota Medical Policy
M. Wellpoint Family of Companies
BlueShield of California (provided as appendix M representative policy) BlueCross BlueShield of Georgia
BlueCross BlueShield of Missouri BlueCross BlueShield of Wisconsin
Unicare
N. The Regence Group Medical Policy
Regence Blue Shield (Washington)
Regence BlueCross BlueShield of Oregon
Regence BlueCross BlueShield of Utah
Regence BlueShield of Idaho
O. Aetna Medical Policy
P. Anthem Medical Policy
Q. Empire BlueCross BlueShield Medical Policy
R. BlueCross BlueShield of Michigan Medical Policy
S. Premera BlueCross Medical Policy
T. CIGNA Healthcare Coverage Position
U. United Healthcare Technical Assessment
V. Highmark BlueCross BlueShield Medical Policy
W. Independence BlueCross Medical Policy
X. BlueCross BlueShield of Florida Medical Policy
Y. BlueCross BlueShield of Kansas City Medical Policy
Z. E:mail correspondence re. BlueCross BlueShield Association National Reference Policy
AA. BlueCross BlueShield of Mississippi
AB. BlueCross BlueShield of South Carolina
AC. BlueCross BlueShield of North Carolina
AD. BlueCross BlueShield of Nebraska
AE. BlueCross BlueShield of Minnesota
AF. BlueCross BlueShield of IL, TX, OK, NM
AG. Excellus BlueCross BlueShield
AH. BlueShield of California
AI. BlueCross BlueShield of Arizona
AJ BlueCross BlueShield of Rhode Island
AK BlueCross BlueShield of Massachusetts
AL BlueCross BlueShield of Tennessee