(19) DANMARK

(10) DK/EP 2976013 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *G 06 T 7/90 (2017.01)* *A 61 B 1/00 (2006.01)* *A 61 B 1/04 (2006.01)* *A 61 B 5/00 (2006.01)* *A 61 B 5/103 (2006.01)* *G 06 T 7/00 (2017.01)*

(45) Oversættelsen bekendtgjort den: **2018-11-05**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2018-07-25**

(86) Europæisk ansøgning nr.: **14710934.2**

(86) Europæisk indleveringsdag: **2014-03-19**

(87) Den europæiske ansøgnings publiceringsdag: **2016-01-27**

(86) International ansøgning nr.: **EP2014055549**

(87) Internationalt publikationsnr.: **WO2014147149**

(30) Prioritet: **2013-03-19 EP 13160048**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **Fremgangsmåde til vurdering af erythema**

(56) Fremdragne publikationer:
EP-A1- 0 434 279
WO-A1-93/16635
WO-A2-2006/106509
WO-A2-2011/106792
US-A- 5 241 468
US-A1- 2005 030 372
H Takiwaki: "Measurement of skin color: practical application and theoretical considerations", The journal of medical investigation : JMI, 1 February 1998 (1998-02-01), page 121, XP055124277, JAPAN Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pubmed/959 7799 [retrieved on 2014-06-19]
A. CHARDON ET AL: "Skin colour typology and suntanning pathways", INTERNATIONAL JOURNAL OF COSMETIC SCIENCE, vol. 13, no. 4, 1 August 1991 (1991-08-01) , pages 191-208, XP055125017, ISSN: 0142-5463, DOI: 10.1111/j.1467-2494.1991.tb00561.x
MARK NISCHIK ET AL: "Analysis of Skin Erythema Using True-Color Images", IEEE TRANSACTIONS ON MEDICAL IMAGING, IEEE SERVICE CENTER, PISCATAWAY, NJ, US, vol. 16, no. 6, 1 December 1997 (1997-12-01), XP011035685, ISSN: 0278-0062

DESCRIPTION

Field of the invention

[0001] The present invention relates to methods for an objective and quantitative erythema documentation and analysis. In particular, the invention relates to a method for assessing erythema of a subject comprising the steps of measuring the light reflectance of a skin or mucosal area of the subject, obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and calculating the erythema value according to the formula $(L^*_{max} - L^*) \times a^*$. Furthermore, the invention relates to a method for assessing the risk of a subject to develop erythema caused by irradiation by calculating the erythema value according to the invention; an according method for predicting the intensity of erythema that a subject develops due to irradiation; an according method for predicting the time until a subject develops erythema caused by irradiation; an according method for testing a pharmaceutical or cosmetic preparation for its ability to cause or treat erythema in a subject; and to an according method for testing a pharmaceutical or cosmetic preparation for its ability to ameliorate the appearance of erythema of a subject. The invention further relates to methods for analyzing skin color of a subject, methods for documenting or analyzing wounds or wound healing of a subject based on the formula $(L^*_{max} - L^*) \times a^*$. In another aspect, the invention relates to methods of analyzing meat based on the formula $(L^*_{max} - L^*) \times a^*$.

Background to the invention

[0002] Skin or mucosal inflammation is often manifested as erythema. Erythema is frequently associated with diaper rash, acne, dermatitis, eczema and other skin or mucosal conditions. Another example of erythema is radiation dermatitis, which is an inflammatory skin reaction associated with prolonged exposure to ionizing radiation.

[0003] Radiation dermatitis occurs to some degree in most patients receiving radiation therapy, with or without chemotherapy. In severe cases it leads to discontinuation of radiation therapy. Acute radiation induced dermatitis is one of the most frequent side effects of radiotherapy. The pathoethiological cause for the reaction is linked to massive ROS production which is induced during irradiation treatment (Beckmann and Flohé 1981) and in the course of chemotherapy (Kasapovic et al. 2010). This ionizing radiation can lead to acute dermatitis in 95% of patients, whereof in 87% of patients moderate to severe radiodermatitis occurs during or at the end of the treatment (Mc Question M 2006). The severity of the skin reaction ranges from a moderate erythema to edema or deep ulcerations. The occurrence of this reaction depends on aspects associated with the therapy (radiation quality, dose per fraction, cumulative dose, fraction scheme, size of the treatment area, concomitant therapy, pre-radiation, localization of irradiated area) and on aspects associated with the patient (skin type, sensitivity to radiation, concomitant diseases). Pruritus, erythema, skin distension, epitheliolysis, and pain affect not

only the quality of life but also pose a risk of an infection of the open wounds. Consequently, this may lead to treatment interruptions or discontinuations of the RTX, and longer deferment of the subsequently planned system therapy. Thus an early detection, precise documentation and treatment of these dermal toxicities are of great importance.

[0004] Furthermore, up to now there is no reliable prognostic parameter available to predict the risk to develop radiodermatitis upon radiation therapy. According to historical data, breast size, smoking history, body mass index (BMI) and comorbidities such as diabetes, rheumatoid arthritis and hypertension are under suspicion to be correlated with an increased risk for the development of radiodermatitis in the course of cancer irradiation therapy (Fernando IN et al., Clin Oncol 1996; 8:226-233). However the published data is conflicting. According to a recent single blind randomized phase III trial in breast cancer patients, no association between dermatitis and BMI or breast size were observed (Pinnix C et al., Int J Radiat Oncol Biol Phys 2012 Jul 15; 83(4): 1089-94), also confirmed by our own data. Furthermore, the radiation field size (cm^2) and the basic skin color according to the Fitzpatrick Scale (1-2 versus 3-4) did not correlate with the risk to develop grade 2 dermatitis (based on the CTCAE, further described below) according to our own data. However, a prognostic marker would allow to prevent or reduce radiation dermatitis by determining or adapting radiation dose and duration, and also to predict the time until a prophylaxis and/or treatment needs to be given.

[0005] So far, erythema is clinically assessed mainly by subjective observation by a physician. For example, the classification system Common Terminology Criteria for Adverse Effects (CTCAE v. 4.03), developed by the Radiation Therapy Oncology Group (RTOG), and the National Cancer Institute (NCI), divides skin reactions and other adverse events into 5 grades, according to the degree of severity. This grading system has already been used in numerous clinical trials. However, the shortcomings of said current clinical classification systems are mainly based on the subjective assessment of the skin condition, which can vary greatly among assessors and may even differ in one assessor in the course of one day or between several days. A further drawback of this method is the classification in only five grades. Thus, minor differences in the skin condition, as needed for clinical comparison of the effectiveness of e.g. topical medication, cannot be sufficiently indicated.

[0006] For a more objective assessment of erythema several devices have been used. For example, chromameters have been utilized for analyzing hemoglobin, since skin or mucosal erythema is primarily due to vasodilation and local increases in hemoglobin concentration. Chromameters give values of standardized parameters for color evaluation: L*, a*, b*, with a* being used as an indicator of the "red" content and therefore related to erythema.

[0007] Spectrophotometers have also been used for analyzing hemoglobin based on diffuse reflectance spectroscopy, according to which the reflected light from skin is collected and analyzed into its spectral components. Spectral analysis algorithms have been used to calculate chromophore concentrations including oxy- and deoxy-hemoglobin (relating to erythema). Various light reflectance devices such as a Mexameter are also known for giving an erythema index.

[0008] The analysis of digital color images of skin has also been utilized for analyzing erythema

[0009] Such methods are described for example in US 8,150,501 and in Jung et al 2005, Lasers in Surgery and Medicine 37:186-191 or US 8,150,501 and Jung et al 2004, Lasers in Surgery and Medicine 34:174-181.

[0010] Another imaging analysis tool for the assessment of erythema is the DermaVision system from the company OptoBioMed (http://www.optobiomed.co.kr/; see also the patent application KR2003083623).

[0011] The wound healing analysis tool (W.H.A.T) is a computer-based method to assess wound healing (see e.g. T. Wild, M. Prinz, N. Fortner, W. Krois, K. Sahora, S. Stremitzer and T. Hoelzenbein (2008). "Digital measurement and analysis of wounds based on colour segmentation". European Surgery 40(1):5-10; and S. Stremitzer und T. Wild (2007). "Digitale Wundanalyse mit W.H.A.T. (Wound Healing Analyzing Tool): Manual der Wundheilung. 15-22; and http://what-tool.com). The W.H.A.T system is based on certain threshold levels for parameters, such as color, which allow categorization and sizing of wound segments (e.g. wound center, wound border) and thus, allows to document wound healing based on the assessment of the decrease of the size of the central wound area, which is defined by certain threshold parameters.

[0012] Nischek et al. (IEEE Transactions on Medical Imaging, vol 16, no 6, 1997) analyse skin erythema using true-color images. Hirotsugu (The Journal of Medical Investigation, vol 44, 1998, pages 121-126) discloses methods for use in measurement of skin color. Document US 2005/030372 A1 (Jung et al.) discloses a method for assessing erythema of a subject.

[0013] All of the methods described above are able to identify erythema or skin redness and to define areas of erythema. However, these techniques show substantial deficiencies in the assessment of erythema intensity. In particular, the prior art methods do not allow a reliable quantitative measurement of various grades of inflammation or the differentiation between several intensities of erythema, especially not for rather low or high intensities of erythema. Thus, the methods of the prior art do neither provide a solid measure for erythema and therewith associated cutaneous alterations over the entire range of intensities nor do they offer a innovative computational techniques linking erythema assessment and erythema documentation with the possibility for remote monitoring of individual subjects or subject areas over varying observation periods.

[0014] Furthermore, H. Takiwaki (1998). "Measurement of skin color: practical application and theoretical considerations": The journal of medical investigation: JMI, 121-126, discloses a similar method for erythema analysis that fails to disclose a similar erythema calculation formula.

[0015] Furthermore, A. Chardon et al. (1991). "Skin colour typology and suntanning pathways": INTERNATIONAL JOURNAL OF COSMETIC SCIENCE, vol.13, no. 4, 191-208, discloses a similar erythema assessment method which also fails to disclose a similar calculation formula. Accordingly, novel objective methods and innovative computational assessment and monitoring tools are urgently needed for reduction of these inter- and intra-observer variability as well as for sensitive and quantitative assessment of the degree of erythema over the entire intensity range and varying observation times.

Brief description of the invention

[0016] In a first aspect, the invention relates to a method for assessing erythema of a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the erythema value according to the formula
  $(L^*_{max} - L^*) \times a^*$.

[0017] In a second aspect, the invention relates to a method for assessing the risk of a subject to develop erythema caused by irradiation comprising the steps of

- measuring the light reflectance of a skin or mucosal area of a subject prior to irradiation,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space,
- calculating the baseline erythema value according to the formula
  $(L^*_{max} - L^*) \times a^*$,

  and
- correlating the baseline erythema value to the risk of the subject to develop erythema caused by irradiation.

[0018] In a third aspect, the invention relates to a method for predicting the intensity of erythema that a subject develops due to irradiation comprising the steps as described above, and correlating the baseline erythema value to the intensity of erythema that the subject develops due to irradiation.

[0019] In a fourth aspect, the invention relates to a method for predicting the time until a subject develops erythema caused by irradiation comprising the steps as described above, and inversely correlating the baseline erythema value to the time until the subject develops erythema caused by irradiation.

[0020] In a fifth aspect, the invention relates to a non-therapeutical method for testing a pharmaceutical or cosmetic preparation for its ability to cause or treat erythema in a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject prior to and following the administration of the pharmaceutical or cosmetic preparation,
- obtaining the L* value and the a* value of each measurement according to the L*a*b* color space, and
- calculating the erythema value for each measurement according to the formula $(L^*_{max} - L^*) \times a^*$.

[0021] In a sixth aspect, the invention relates to a non-therapeutical method for testing a pharmaceutical or cosmetic preparation for its ability to ameliorate the appearance of erythema of a subject comprising the steps as described above.

[0022] In an example, a method relates to analyzing skin color of a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the skin redness value according to the formula $(L^*_{max} - L^*) \times a^*$.

Brief description of the figures

[0023]

Figure 1: Graphical representations of the L*a*b* color space.

Figure 2: Original photo and pseudo grey scale images based on the a* value and on the erythema value calculated by the novel algorithm the for improved visualization of erythema.

Figure 3: L*a*b* parameters and their change over treatment time.

Figure 4: Erythema values over treatment time (A) and correlation to the subjectively assessed radiodermatitis grade (B).

Figure 5: Erythema values over treatment time, separated for the patient population of a grade 2 (A) and grade 0-1 (B) radiodermatitis. The threshold erythema values for grade 2 and 3 are given based on the subjective erythema grading.

Figure 6: Red color gradient (A) and calculated imaging variants based on an image with 8 bit per channel according to the L*a*b* color space (B).

Figure 7: Table comprising the color gradient as well as all values of the RGB and L*a*b* color space underlying said red color gradient.

Figure 8: Yellow color gradient (A) and calculated imaging variants based on an image with 8 bit per channel according to the L*a*b* color space (B).

Figure 9: Table comprising the color gradient as well as all values of the RGB and L*a*b* color space underlying said yellow color gradient.

Figure 10: Using a software app integrating the invented methods to analyse erythema values of Naevus lenticularis areas in a phase I trial (A) and time dependent changes of analyzed erythema values (B)

Detailed description of the invention

[0024] The invention provides methods for analyzing skin color and methods for assessing erythema based on measuring the light reflectance of a skin or mucosal area and analyzing said measurement by using a novel formula to calculate the erythema value. The skin redness or erythema value provides an objective, continuous measure for skin redness or erythema over the entire range of intensities. Accordingly, the higher the skin redness erythema value the higher is the intensity of erythema.

[0025] The term "erythema" as used herein may comprise any skin or mucosal redness, or skin or mucosal irritation, or skin lesions. For example, erythema may include dermatitis (e.g. radiodermatitis), eczema, epitheliolysis, desquamation, redness, rubor, and/or rash. Erythema may also comprise any type of erythema, such as erythema ab igne, erythema chronicum migrans, erythema induratum, erythema infectiosum, erythema marginatum, erythema migrans, erythema multiforme, erythema nodosum, erythema toxicum, keratolytic winter erythema, palmar erythema, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, also known as "Lyell's syndrome") and Naevus flammeus nuchae. The term "erythema" further refers to skin lesions or wounds. The term "erythema" may also include wounds of any stage, i.e. fresh wounds, as well as wounds in different stages of wound healing.

[0026] Erythema may affect one or more layers of skin or mucosa, e.g. one or more layers of the epidermis and/or one or more layers of the dermis; or one or more layers of the mucous membranes, e.g. the mucosal epithelium (Lamina epithelialis mucosae) and/or the Lamina propria or the conjunctive tissue (e.g. sclera; conjunctiva of the eye).

[0027] The term "using a software application" as used in our invented methods can be

recognized and understood in any context interchangeable for using a software app, or using an application program or using an application or using an app or a software tool or a web software or in more general words, the use of any software allowing to perform useful tasks which go beyond the running of the computer itself allowing the integration of our invented computational methods.

[0028] In a first aspect, the invention relates to a method for assessing erythema of a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the erythema value according to the formula $(L^*_{max} - L^*) \times a^*$.

[0029] In a second aspect, the invention relates to a method for assessing the risk of a subject to develop erythema caused by irradiation comprising the steps of

- measuring the light reflectance of a skin or mucosal area of said subject prior to irradiation,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space,
- calculating the baseline erythema value according to the formula $(L^*_{max} - L^*) \times a^*$,

  and
- correlating said baseline erythema value to the risk of the subject to develop erythema caused by irradiation.

[0030] In a third aspect, the invention relates to a method for predicting the intensity of erythema that a subject develops due to irradiation comprising the steps of

- measuring the light reflectance of a skin or mucosal area of said subject prior to irradiation,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the baseline erythema value according to the formula $(L^*_{max} - L^*) \times a^*$,

  and
- correlating said baseline erythema value to the intensity of erythema that the subject develops due to irradiation.

[0031] In a fourth aspect, the invention relates to a method for predicting the time until a subject develops erythema caused by irradiation comprising the steps of

- measuring the light reflectance of a skin or mucosal area of said subject prior to irradiation,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space,
- calculating the baseline erythema value according to the formula
  $(L^*_{max} - L^*) \times a^*$,

  and
- inversely correlating said baseline erythema value to the time until the subject develops erythema caused by irradiation.

In an embodiment of the second, third and fourth aspect, the light reflectance of a skin or mucosal area of the subject is measured prior to irradiation. With regard to said embodiments, the term "prior to irradiation" refers to a time-point prior the start of irradiation exposure or at the beginning of irradiation, i.e. prior to the first irradiation, which may be a first irradiation in a course of several subsequent irradiations. The according erythema value is calculated based on said baseline measurement and is a baseline erythema value. The light reflectance of a skin or mucosal area of the subject may be measured at two or more time-points prior to irradiation, and an according mean baseline erythema value may be calculated. In an embodiment of the second, third and fourth aspect, the light reflectance of a skin or mucosal area of the subject is measured at one or more time-points following irradiation. The term following irradiation with regard to said aspects refers to one or more time-points within the initial period of irradiation, in particular, during the phase of the first few exposures to irradiation, or during the first few days of irradiation therapy. For example, the light reflectance of a skin or mucosal area of the subject is measured at one or more days during the first week of radiation therapy. The one or more erythema values are calculated based on said initial measurements, and may be defined as initial erythema values.
The term "correlating" as used herein refers to a direct relation of the erythema value to the respective other parameter. For example, the higher the baseline erythema value of a subject, the higher is the risk of the subject to develop erythema caused by irradiation, and/or the intensity of erythema that the subject develops due to irradiation.
The term "inversely correlating" as used herein refers to an inverse relation of the erythema value to the respective other parameter. For example, the higher the baseline erythema value of a subject, the shorter is the time until the subject develops erythema caused by irradiation, or the lower the baseline erythema value of a subject, the longer is the time until the subject develops erythema caused by irradiation.

[0032] The gradient between said baseline and/or initial erythema values may be calculated, e.g. between the baseline erythema value and one or more of said initial erythema values, or between two or more initial erythema values. The baseline erythema value, as well as said gradient may be correlated to the risk to develop erythema caused by irradiation, to the intensity of erythema caused by irradiation, or may be inversely correlated to the time until a

subject develops erythema caused by irradiation. Accordingly, either the baseline erythema value, or the gradient between two or more erythema values, or a combination of both may be used to assess or predict these parameters. In one embodiment, the light reflectance is measured prior to irradiation and at one or more time-points following irradiation, the gradient between two or more erythema values is calculated, and said gradient is correlated to the risk of a subject to develop erythema caused by irradiation, or to the intensity of erythema that the subject develops due to irradiation, or inversely correlated to the time until the subject develops erythema caused by irradiation. In another embodiment, the risk of a subject to develop erythema caused by irradiation, the intensity of erythema that the subject develops due to irradiation, or the time until the subject develops erythema caused by irradiation is assessed or predicted based on the baseline erythema value and on the gradient between two or more erythema values.

[0033] In one example a prognosis for the subject is given for all three parameters based on one or more baseline and/or initial erythema values. Accordingly, the risk of the subject to develop erythema caused by irradiation is assed based on calculating the baseline and/or initial erythema value according to the invention and correlating it to said risk, the intensity of erythema that the subject develops due to irradiation is predicted based on calculating the baseline and/or initial erythema value according to the invention and correlating it to said intensity, and the time until the subject develops erythema caused by irradiation is predicted based on calculating the baseline and/or initial erythema value according to the invention and inversely correlating it to said time.

[0034] In a fifth aspect, the invention relates to a non-therapeutical method for testing a pharmaceutical or cosmetic preparation for its ability to cause or treat erythema in a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject prior to and following the administration of said pharmaceutical or cosmetic preparation,
- obtaining the L* value and the a* value of each measurement according to the L*a*b* color space, and
- calculating the erythema value for each measurement according to the formula $(L^*_{max} - L^*) \times a^*$.

[0035] In a sixth aspect, the invention relates to a non-therapeutical method for testing a pharmaceutical or cosmetic preparation for its ability to ameliorate the appearance of erythema in a subject comprising the steps of

- measuring the light reflectance of a skin area of the subject prior to and following the administration of said pharmaceutical or cosmetic preparation,
- obtaining the L* value and the a* value of each measurement according to the L*a*b* color space, and
- calculating the erythema value for each measurement according to the formula

$(L^*_{max} - L^*) \times a^*$.

[0036] In an example of the fifth or sixth aspect, the light reflectance of a skin or mucosal area of said subject is measured at least once prior to administration of the pharmaceutical or cosmetic preparation, and at one or more time-points following the administration pharmaceutical or cosmetic, and the erythema values are calculated for each measurement. The term "following the administration of said pharmaceutical or cosmetic preparation" with regard to said aspects refers to one or more time-points within and/or after the period of administration of the pharmaceutical or cosmetic preparation. For example, the light reflectance of a skin or mucosal area of the subject is measured at one or more time-points after single or repeated administration of the pharmaceutical or cosmetic preparation. The light reflectance of a skin or mucosal area of the subject may also be measured at one or more time-points after the period administration of the pharmaceutical or cosmetic preparation, i.e. when the pharmaceutical or cosmetic preparation is no longer administered. The gradient between two or more of said erythema values may be determined, e.g. between two or more subsequent measurements or erythema values, or between two or more measurements or erythema values over treatment or observation time. An increase of the erythema value between two or more erythema values over administration time indicates progression of erythema, i.e. that the pharmaceutical or cosmetic preparation causes erythema, or is not effective in preventing erythema. No significant change of the erythema value between two or more erythema values over administration time indicates a stable skin or mucosal condition, i.e. that the pharmaceutical or cosmetic preparation does not cause erythema, is effective in preventing erythema, is not effective in treating erythema, or is not effective in ameliorating the appearance of erythema. A decrease of the erythema value between two or more erythema values over administration time indicates regression of erythema, i.e. that the pharmaceutical or cosmetic preparation is effective in treating erythema, or in ameliorating the appearance of erythema.

[0037] In an example of the sixth aspect, the opacity of a cosmetic product is tested. The cosmetic product may be make-up, a foundation, face powder, camouflage, a cover stick, or a concealer. A decrease of the erythema value after application of the product indicates that the cosmetic product is effective in covering erythema.

[0038] In an example, a method relates to analyzing skin color of a subject comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the skin redness value according to the formula
  $(L^*_{max} - L^*) \times a^*$.

[0039] In a major aspect of the above given invention the term "skin color" refers to skin or mucosal or conjunctiva color comprising any shades of red, especially skin redness or mucosal redness. Such skin redness includes healthy skin or mucosa or conjunctiva and irritations of the skin or mucosal or conjunctiva, such as e.g. erythema. Accordingly, the term "skin redness value" refers to the value calculated based on the measurement of skin or mucosal color. For example, the skin redness value may be defined as erythema value and referring to such aspect local or time dependent differences in the erythema value can be used to objectively analyze and interpret changes in context to Lentigo solaris or Lentigo simplex or Lentigo maligna or Lentigo aestiva of a subject.

[0040] In another aspect the definition "skin color" refers to skin or mucosa or conjunctiva color comprising erythema shades and further comprising shades of yellow pigmentation, especially in the skin or sclera (white of the eye). Such yellowish skin pigments are included in the normal healing process of a skin hematoma or can be observed in context to life threatening diseases e.g. Icterus (Jaundice). Slightly increased levels of bilirubin, the yellow breakdown product of haeme catabolism, is visually noticeable in the sclera at bilirubin levels of about 2 to 3 mg/dL (34 to 51 µmol/L) but much higher Bilirubin levels are required for reliable icterus assessment of the skin due to masking effects of normal skin pigmentation. Normal skin pigmentation however is considered in our method by obtaining the L* and b* value and calculating the yellowness value of the skin or mucosa according to the formula $(L^*_{max} - L^*) \times b^*$ providing a novel sensitive and non invasive method for objective documentation and assessment of icterus grading and development of a subject over time.

[0041] In another aspect the method may be used to assess the ability of a cosmetic preparation to tan the skin of a subject, i.e. to test a skin tanning preparation. Accordingly, the skin redness value (including the information of brightness, i.e. also considering the skin tanning) is calculated based on one or more measurements of a treatment area prior to and after the administration or usage of a skin tanning preparation. In said embodiment, the reference area may be an area that is not a treatment area, i.e. not covered by the cosmetic preparation.

[0042] In a more distant aspect the method may be used for analyzing meat.

[0043] In one embodiment of the present invention, the subject is a human. In one embodiment, the human is a Caucasian. In another embodiment, the subject is a non-human animal. The non-human animal may be a non-human mammal selected from the group consisting of non-human primates, pigs, rodents, or rabbits. In an embodiment, the subject is a pig, such as a minipig. In another embodiment, the subject is a nude mouse. In one embodiment, the subject is a human female breast cancer patient who receives radiation therapy. The breast cancer patient may have undergone surgery, e.g. breast-preserving surgery. In one embodiment, the subject is a human head and neck cancer (HNC) patient who receives radiation therapy. The HNC patient may have undergone surgery. In an embodiment, the subject is treated with chemotherapy.

[0044] In an example, the subject is or will be treated with a treatment that may cause erythema, or is prone to erythema. In another example, the subject is or will be treated with a treatment that may cause erythema, or is prone to erythema, and is or will be treated with a treatment that prevents erythema. In still another embodiment, the subject is suffering from erythema and is or will be treated with a treatment that may treat erythema and/or ameliorate the appearance of erythema.

[0045] In an example, the subject is or will be exposed to irradiation, or is suffering from or prone to radiation induced dermatitis or sunburn.

[0046] In one example, the subject is or will be treated with cytotoxic drugs, such as e.g. fluorouracil, capecitabine, cytarabine, sorafenib, or pegylated liposomal doxorubicin (Doxil), or tyrosine kinase inhibitors (e.g. sorafenib and sunitinib). For example, the subject may suffer from or is prone to palmar-plantar erythrodysesthesia or hand-foot syndrome.

[0047] In an example, the subject is or will be treated with a drug that may cause erythema, such as e.g. antibiotics (sulfonamides, penicillins, cefixime), barbituates, lamotrigine, phenytoin (e.g., Dilantin), nonsteroidal anti-inflammatory drugs (NSAIDs); or EGFR inhibitors. For example, the subject is or will be treated with an anti-EGFR antibody therapy, especially with cetuximab (Erbitux®).

[0048] In an example, the subject is or will be exposed to one or more allergens, such as e.g. various allergens for allergy testing, urushiol (a resin produced by poison ivy and poison oak), penicillin, latex, or wasp, fire ant and bee stings.

[0049] In an example, the subject is suffering from a fungal infection, such as e.g. tinea (ringworm), or candida.

[0050] In an example, the subject is suffering from a bacterial infection, e.g. with staphylococcus, streptococcus, or by a treponemal disease, such as e.g. syphilis, bejel, pinta and yaws.

[0051] In an example, the subject is suffering from a viral infection, which may be selected from the group consisting of shingles, rubella, herpes, hand-foot-mouth disease, enterovirus infection, chickenpox infection, or infection by erythrovirus (erythema infectiosum or fifth disease).

[0052] In an example, the subject is suffering from a skin disease, which may be selected from the group consisting of psoriasis, atopic eczema or atopic dermatitis (neurodermatitis), eczema, or acne.

[0053] In an example, the subject is suffering from a disease affecting internal or external mucosa, e.g. oral, nasal, or intestinal mucosa. For example, the subject is suffering from

inflammatory bowel disease, Morbus Crohn (or Crohn's disease), aphthous stomatitis, conjunctivitis, chronic obstructive pulmonary disease, peptic ulcers, alcohol abuse, or gastritis.

[0054] In an example, the subject is suffering from a somatoform disorder, such as blushing.

[0055] In an example, the subject will have or has one or more wounds. Said wounds may be of any origin (e.g. surgery or injury), as well as of any stage, i.e. fresh wounds or wounds in any stage of wound healing. A wound is a type of injury in which skin is torn, cut, or punctured (an open wound), or where blunt force trauma causes a contusion (a closed wound). In particular, a wound is an injury which damages the epidermis and/or dermis of the skin. However, the wound may also be a mucosal lesion or injury. In general, the wound may affect one or more layers of skin or mucosa, e.g. one or more layers of the epidermis and/or one or more layers of the dermis; or one or more layers of the mucous membranes, e.g. the mucosal epithelium (Lamina epithelialis mucosae) and/or the Lamina propria.

[0056] Thus, in an example, the method can be applied for documenting or analyzing wounds or wound healing of a subject or for documenting hematoma intensity or hematoma development of the skin or mucosa or conjunctiva of a subject over time. This may be done with the inventive method comprising the steps of

- measuring the light reflectance of a skin or mucosal area of the subject,
- obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and
- calculating the erythema value according to the formula $(L^*_{max} - L^*) \times a^*$.

[0057] In one embodiment, the skin or mucosal area is a skin area. In another embodiment, the skin or mucosal area is a mucosal area. The mucosal area may be an external or internal mucosa, e.g. nasal, oral, intestinal mucosa. In an example, the skin or mucosal area is a gross area comprising one or more segment areas. In said example, each step of the methods of the invention is done separately for each segment area. Accordingly, the erythema value is calculated for each segment area according to the invention.

[0058] In one example, the erythema value or any other skin color value may be calculated separately for each subarea. A subarea may a subarea as described below, or -if the light reflectance of a skin or mucosal area is measured by obtaining an image, a subarea may also be a single pixel of said image, i.e. the erythema value is calculated for one or more single pixels. Accordingly, a mean erythema value or a mean value of any other skin color value may be calculated of one or more single pixels of the image, the gross area, and/or the segment area.

[0059] The segment area may be an erythema area (or a representative part of an erythema area). In one embodiment, the erythema area is an area being prone to erythema, which may

e.g. be caused by a disease and/or treatment as further described below. In another embodiment, the erythema area is an area characterized by erythema. Said erythema may have been caused by a disease and/or treatment as further described below. The term "treatment" must be realized in this context as a required therapeutic treatment of a subject which may be a local treatment (e.g. of the skin or mucosal area of the subject), or a systemic treatment of the subject (e.g. a treatment with an anti-EGFR antibody). Accordingly, in an embodiment, the segment area prone to erythema or characterized by erythema may be the analyzed treatment area of a local treatment, or the analyzed area at which the erythema occurs upon systemic treatment.

[0060] The analyzed segment area may also be a treatment area (or a representative part of a treatment area), i.e. an analyzed area that is or will be physically and/or chemically treated, e.g. with irradiation (including but not limited to x-ray, ultraviolet, and/or solar irradiation), and/or with a pharmaceutical and/or cosmetic preparation. In one example, the analyzed erythema area is also a treatment area. In an embodiment, the irradiation is radiotherapy, especially fractionated radiotherapy.

[0061] An analyzed segment area may also be a reference area (or a representative part of a reference area). Said reference area may be an area of the same subject. In an example, the reference area may be an area of one or more subjects other than the subject to be assessed. Said different subjects may be of the same race (e.g. Caucasian), of the same or similar skin color, and/or of the same skin type (e.g. according to the Fitzpatrick Skin Scale). In an example, said different subjects have the same kind of skin condition, e.g. erythema. In still another embodiment, said different subjects suffer from the same or a similar disease and/or undergo the same or similar treatment. Accordingly, a reference curve of two or more reference erythema values may be generated for comparison to the subject's measurements. In general, for any comparison of erythema values (e.g. to reference values), the area under the curve between two or more erythema values may be determined and compared to e.g. the area under the curve of two or more reference erythema values.

[0062] Furthermore, The reference area may be an area similar to the erythema and/or treatment area, i.e. an area of the same or a similar region of the body, and/or of the same or similar nature (e.g. of similar color and/or shape). In one example, the reference area is adjacent to the segment area to be compared to, e.g. the erythema and/or treatment area. In one example, the reference area is of the same size as the segment area to be compared to, e.g. the erythema and/or treatment area. The erythema value calculated for a reference area may also be called reference erythema value. In an embodiment, the reference area is not an erythema area, for example, if the method of the present invention is used to assess a treatment that may cause erythema. In said example, the reference area is not characterized by erythema, i.e. is free from erythema. For example, the reference area may be the treatment area prior to treatment with a preparation or treatment that may casue erythema, thus, prior to development of erythema. In one example, the reference area is not a treatment area. In an example, the reference area is left completely untreated. In a further example, the reference area is treated with a placebo or with a reference treatment, such as e.g. the gold standard

treatment or a competitive or comparative product. In another example, the reference area is characterized by erythema, for example, if the method of the present invention is used to assess a treatment that may ameliorate erythema. In another example, the reference area is an erythema and/or treatment area prior to development of erythema and/or prior to treatment. The reference erythema value calculated for a reference area that is an erythema and/or a treatment area, but based on a measurement prior to development of erythema and/or prior to treatment, may also be called baseline erythema value or initial erythema value.

[0063] In an embodiment, the erythema value is compared to a reference erythema value. For example, the erythema value of a segment area (e.g. a treatment and/or erythema area) is compared to one or more reference erythema values. In one example, the reference erythema value is calculated based on one or more reference areas. In another example, the reference erythema value is the erythema value of the same segment area from which the follow-up erythema value is calculated, e.g. an erythema and/or treatment area, assessed prior to treatment and/or development of erythema.

[0064] In another example, the erythema value may be compared to more than one reference erythema values and/or one or more reference gradients between two or more erythema values of reference areas. Said reference erythema values and/or reference gradients may include reference erythema values of the same subject or of one or more different subjects. For example, a reference erythema gradient, or a rating or reference curve may be determined from subjects with the same or similar type and/or grade of erythema, e.g. with the same disease or treatment. Accordingly, the erythema of a subject may be assessed by calculating one or more erythema values according to the invention and comparing said one or more erythema values to one or more reference erythema values, a reference erythema gradient between two or more reference erythema values, and/or to a rating or reference curve.

[0065] The light reflectance of the skin or mucosal area may be measured by using an imaging method, such as digital photography. Accordingly, in an embodiment, the light reflectance of a skin or mucosal is measured by obtaining an image of said skin or mucosal area. The image may be a raster graphics image (or bitmap). Accordingly, in one example, the steps of obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and calculating the erythema value according to the formula of the invention are done per pixel, i.e. separately for one or more pixels of the skin or mucosal area. For example, the image may comprise a gross area comprising one or more segment areas, and the erythema values are calculated for one or more pixels of said area. The erythema value may be calculated for all pixels that are representative of said skin or mucosal area, or of each pixel of said skin or mucosal area. The erythema value may be calculated for each pixel of the image. Optionally, one or more pixels may be excluded, e.g. any pixels of non-representative subareas may be excluded, as further described below. Based on the single pixel erythema values, a mean erythema value may be calculated for the skin or mucosal area. In an example, the mean erythema value is the arithmetic mean of single pixel erythema values of the skin or mucosal area.

[0066] In one embodiment, the light reflectance is measured in the L*a*b* color space and the L* value and the a* value are obtained directly from said measurement.

[0067] In another embodiment, the light reflectance is measured in a color space other than the L*a*b* color space, and the L* value and the a* value according to the L*a*b* color space are obtained by converting the light reflectance values of said measurement into the corresponding values of the L*a*b* color space.

[0068] In one example, the light reflectance values of one or more pixels of the image according to the color space of the measurement are obtained directly from the image file. In an example, the light reflectance values of each single pixel of the image are obtained. In another embodiment, said one or more single pixel values are obtained by using a graphics software, such as Adobe Photoshop, Corel Paint Shop, Corel Photo Paint, Irfan View, GIMP, Paint.NET, or the like.

[0069] In one example, a mean erythema value based on single pixel erythema values is calculated for each segment area. In one embodiment, a mean erythema value based on single pixel erythema values is calculated for each reference area. In another embodiment, a mean erythema value based on single pixel erythema values is calculated for each gross area. Furthermore, a mean erythema value may be calculated for more than one segment areas, reference areas, and/or gross areas. The mean erythema value may comprise all single pixel erythema values of the skin or mucosal area, e.g. the segment area. However, in an example, one or more single pixel erythema values may be excluded from the calculation of the mean erythema value.

[0070] In general, any of the above described methods for measuring the light reflectance of a skin or musosal area may be combined with laser scanning, such as e.g. 3D laser scanning, to obtain further information of the skin or mucosal area, such as the 3D structure.

[0071] In one example, the erythema area is a treatment area that is or will be (locally) treated with a physical and/or chemical treatment that may cause erythema. For example, the physical and/or chemical treatment may be selected from the group consisting of irradiation, systemic treatment (e.g. subcutaneous, mucosal, intramuscular injections), or topical treatment (including mucosal administration) with a pharmaceutical and/or cosmetic preparation, allergy tests, such as e.g. a Prick test, and/or a patch test. In said example, the erythema area is an area prone to erythema. Furthermore, in said example, the erythema area is also a treatment area. In said example, a respective reference area is not characterized by erythema. Accordingly, the reference area may be the same area as the erythema area, but prior to treatment. If the reference area is an area other than the erythema area, the reference area is not a treatment area.

[0072] In an example, the treatment area is an erythema area characterized by erythema that is or will be treated with a pharmaceutical or cosmetic that may ameliorate the erythema, e.g. a

preparation comprising one or more antibiotic, anti-inflammatory, wound-healing, and/or anti-oxidant agents. In said example, the reference area is an erythema area characterized by erythema that is not a treatment area, i.e. that is not treated with the pharmaceutical or cosmetic. In one embodiment, the anti-oxidant agent is superoxide dismutase (SOD), especially recombinant human Cu/Zn SOD, optionally in a liposomal formulation.

[0073] In another example, the treatment area is an erythema area characterized by erythema that is or will be topically treated with a cosmetic preparation to cover the erythema, e.g. a preparation comprising one or more pigments, such as make-up, foundations, face powder, camouflage, cover sticks, concealers. In said example, the method may be used to assess the opacity of the cosmetic preparation. In said example, the reference area is an erythema area characterized by erythema that is not a treatment area, i.e. not covered by the cosmetic preparation.

[0074] In another example, the treatment area is an area prone to erythema (e.g. an area that is or will be exposed to sun) that is or will be topically treated with a cosmetic preparation to prevent erythema, e.g. a sun care preparation. In said example, the method according to the present invention may be used to assess the ability of the cosmetic preparation to prevent sunburn. In said example, the reference area may be an area that is or will be exposed to sun that is not a treatment area, i.e. not covered by the cosmetic preparation.A segment area may be determined and/or analyzed based on a software, such as a computer-based manual selection or de-selection tool (e.g. a graphic selection or de-selection tool, for example, a linear, circular, elliptical, rectangular, or polygonal selection or de-selection tool), and/or an automated or semi-automated pattern recognition and/or analysis software (or image recognition and/or analysis software). For example, certain representative areas may be selected and/or certain non-representative areas may be deselected. An example of a semi-automated image analysis is the above referenced Wound Healing Analyzing Tool (W.H.A.T) software.

[0075] In general, certain subareas may be excluded from a segment area and/or the gross area. Accordingly, such subareas may be excluded from the calculation of the respective EV.

[0076] In an example, one or more subareas are manually or automatically excluded from the segment and/or gross area. Such subareas may be any non-representative area (e.g. a border area), or an area with a pigmentation, shade, and/or shape different from the remaining area to be analyzed. The subarea may e.g. be characterized by a scar, a nevus, a freckle, an age spot, a skin fold (e.g. the inframammary fold (IMF), also called inframammary crease or inframammary line), an acromastium, a shadow, a plaster, and/or a mark (such as a patch, a tattoo, an ink mark, e.g. a radiation mark), or parts thereof. Such subareas may be excluded by a computer-based manual selection or de-selection tool (e.g. a graphic selection or de-selection tool, for example, a linear, circular, elliptical, rectangular, or polygonal selection or de-selection tool), and/or by using automated or semi-automated image recognition techniques, such as a pattern recognition software (or an image recognition software).

[0077] A representative part of a segment area may be a subarea of said segment area that shows the main characteristics of the segment area. A representative part of a segment area may be a central subarea of said segment area. Such representative part of a segment area may not include any border areas, e.g. border areas to the surrounding areas, e.g. other segment areas. A representative part of a segment area may also be a segment area, from which one or more non-representative subareas have been excluded. In general, two or more segment areas may or may not overlap. For example, two or more segment areas may partially overlap. Also, any non-representative area may overlap with two or more segment areas, and thus, may be excluded from the gross area comprising said two or more segment areas.

[0078] If the light reflectance is measured by obtaining an image of the skin or mucosal area, the above described selection or de-selection of subareas can be applied to the pixels of the image, i.e. one or more or all pixels of a non-representative subarea may be deselected, or one or more or all pixels of a representative subarea may be selected. Accordingly, said one or more pixels of the non-representative subarea may be excluded from calculating the erythema value, e.g. from calculating the single pixel erythema value and/or the mean erythema value for the segment area. Furthermore, said one or more pixels of the representative subarea may be included into the calculation of the the erythema value or any other color value, e.g. the single pixel erythema value and/or the mean erythema value for the segment area.

[0079] In one example, the gross area comprises at least one erythema and/or treatment area. In one embodiment, the gross area comprises at least one reference area. In one example, the gross area comprises at least one erythema and/or treatment area, and at least one reference area.

[0080] The gross area and/or the segment area may be a predetermined area. The gross area and/or the segment area may be marked, e.g. by one or more patches, tattoos and/or ink marks.

[0081] The light reflectance of a skin or mucosal area may be measured or represented in any color space, i.e. the measurement method or imaging method (and thus, the representation of the measurement or image) may be based on any color space (or color model), such as e.g. the CIE-Lab (or L*a*b*) color space, the XYZ color space, the Yxy color space, the Luv color space (e.g. the CIE-Luv color space, also designated L*u*v*), the RGB color space, the RYB color space, the CMYK color space, HSL, HSV and/or the CIECAM02 color space. The L*a*b*, the XYZ, and the Luv color spaces are independent of the device, with which the light reflectance is measured. In one embodiment, the light reflectance of a skin or mucosal area is measured in the L*a*b* color space. The measurement or image is represented in the L*a*b* color space and the parameters or values are L* (brightness), a* (red/green) and b* (blue/yellow). In said embodiment, the erythema value can directly be calculated based on the actually measured values for brightness (L*values) and redness (a* values). If the light reflectance of a skin or mucosal area is measured in a color space other than the L*a*b* color space, and the measurement or image is represented in a color space other than the L*a*b*

color space, the actually measured values (or parameters) are converted into the respective values of the L*a*b* color space. For example, a measurement or image in the RGB or CMYK color space may be converted into the L*a*b* color space. The RGB or CMYK values first need to be converted to a specific absolute color space, such as sRGB or Adobe RGB. This adjustment may be device dependent, but the resulting data from the transformation may be device independent, allowing data to be converted to the CIE 1931 color space and then converted into L*a*b*. Methods and tools for conversion of values between different color spaces are provided e.g. by the ColorSync service program of Apple, the "Convert to Profile dialog" in Adobe Photoshop (http://www.photoshop.com/), and the easy RGB color calculator (http://www.easyrgb.com/).

[0082] The color space may be the L*a*b* color space, as approved by the French Commission Internationale de l'Èclairage (CIE) (also designated CIE 1976 L*a*b* or CIELAB; see e.g. ONORM EN ISO 11664-4:2008, edition 2012-05-15). It describes all the colors visible to the human eye and was created to serve as a device-independent model to be used as a reference. The three coordinates of the color space represent the lightness of the color (L*= 0 yields black and L*= 100 indicates diffuse white), its value between red and green (a*, negative values indicate green while positive values indicate red), and its value between yellow and blue (b*, negative values indicate blue and positive values indicate yellow). The color saturation increases with increasing distance of the center. Accordingly, each color can be represented in said three-dimensional color system by one single point, i.e. each color can be represented by the three parameters (or coordinates). Figure 1 shows two graphical representations of the L*a*b* color space.

[0083] With reference to the CIELAB color space the a* scale ranges from maximal green saturation (a_{min}) to maximal red saturation (a_{max}) whereas the b* scale ranges from maximal blue saturation (b_{min}) to maximal yellow saturation (bmax). In the present method the maximal values (i.e. L_{max}, a_{max}, and b_{max}) and the minimal values (a_{min} and b_{min}) are determined on the one hand by the measurement method or imaging method and on the other hand by the respective color space and its color depth. The color depth (or bit depth) is the number of bits used to indicate the color of a single pixel of a bitmap, video frame buffer, or image. This concept is usually quantified as bits per pixel (bpp), which specifies the number of bits used. Color depth is only one aspect of color representation, expressing how finely levels of color can be expressed (also known as color precision); the other aspect is how broad a range of colors can be expressed (the gamut). The definition of both color precision and gamut is accomplished with a color encoding specification which assigns a digital code value to a location in a color space.

[0084] In one example, the light reflectance is measured in a single spot measurement. From such single spot measurement, one single L* value and one single a* value are obtained, and the erythema value is calculated based on said single spot values. In another example, the light reflectance is measured by obtaining an image of the skin or mucosal area. Said image comprises multiple pixels and each pixel is defined by the color parameters of the color space in which the measurement is taken. Thus, each single spot measurement or each pixel of a

measurement or of an image may be defined by the parameters or values of the respective color space, e.g. the L*a*b* color space. If the single spot measurement or single pixel is defined by parameters or values of a color space other than the L*a*b* color space, the parameters or values are converted into the L*a*b* color space, as described above.

[0085] For example, the measurement method is spectrophotometry. Spectrophotometry is a single spot measurement, i.e. the skin or mucosal area is measured in one spot. The area which is measured in said spot is predefined by the target mask of the spectrophotometer. In an embodiment, the spectrophotometer has 32 diodes measuring the spectrum of about 400 to 700 nm in 10 nm steps. The spectrophotometry may be based on the L*a*b* color space. Accordingly, this single spot spectrophotometric measurement results in one single L*, a*, and b* value according to the L*a*b* color space. In one example, the data obtained from the spectrophotometer are directly provided in the L*a*b color space. In an example, the spectrophotometer has a maximal value of brightness, i.e. L_{max}, of 100. In said example, the maximal value of redness, i.e. a_{max}, is 127 (see Figure 1 B).

[0086] In another example, the measurement method or imaging method is digital photography. The color depth may e.g. be 8, 12, 15, or 16 bit per channel (or per color parameter). In an embodiment, the color depth is 8 bit per channel, i.e. 24 bit in total. If the color depth is 8 bit per channel, there are 256 possible values for each parameter (L*, a*, and b*). Accordingly, in said example the maximal L* value is 255 (since the lowest value is 0). The a* value representing the two colors red and green also comprises 256 possible values (i.e. 0-255). Thus, the minimal value for red is 128 and the maximal value for red is 255. The maximal value for brightness and redness may be calculated accordingly for any given color depth and/or color space. Based on said maximal L* and a* values, the calculated erythema values may be normalized.

[0087] The measurement or image may be obtained by any suitable measurement method or imaging method, such as e.g. spectrophotometry, video, video frame buffer, and/or photography. For example, the measurement or image may be obtained by a method not requiring any direct contact with the gross area and/or segment areas, e.g. photography. In an embodiment, the measurement or image is obtained by spectrophotometry and/or photography. In an example, the measurement or image is obtained by digital photography.

[0088] In one example, the image is obtained by using the CM-700d spectrophotometer from Konica Minolta. In one embodiment, the image is obtained by using the digital camera Canon powershot G12 from Canon. In one example, the image is obtained by using a digital camera and the SOLIGOR ring flash from Canon.

[0089] For example, the spectrophotometry may be single spot spectrophotometry. The spectrophotometric measurement may be done under standardized conditions. For example, the personnel conducting the measurement is allocated and trained accordingly, the gross are to be measured may be standardized (e.g. predefined), the illumination area (i.e. the measurement area) is predefined (e.g. by a 8 mm target mask), and the spectrophotometer is

calibrated prior to each measurement (e.g. an automatic white balance is done prior to each measurement).

[0090] In another example, the photography is digital photography. The measurement or image may be obtained by using one or more devices selected from the group consisting of a digital camera, a flash (e.g. a ring flash), and a spectrophotometer.

[0091] The measurement or image may also be obtained by using endoscopic devices. In one embodiment, the skin or mucosal area is an internal mucosal area and the light reflectance is measured by endoscopic methods. For example, the methods according to the present invention may be used to diagnose and monitor diseases affecting internal mucosa and their treatment, such as e.g. Morbus Crohn.

[0092] The image may be obtained under standardized conditions, such as the imaging method and equipment, the settings of the imaging devices, the positioning of the object and the imaging device (i.e. the image perspective), and the light exposure. For example, a flash may be used for standardization to improve color contrast and to reduce shading effects. In an example in which several images are compared (e.g. several images of the same area at different time-points, and/or several images of different areas, either at the same or at different time-points), the images may be obtained in the same room, in which the lamps are on (either all available lamps or certain predefined lamps), and in which the window curtains and/or shades are closed (either all available window curtains and/or shades or certain predefined window curtains and/or shades). In one example, the internal flash of the camera is deactivated and a standardized external flash is activated. This is especially important if different cameras are used for several images. The settings of the imaging device may be standardized, such as e.g. the image size, image format, image color scheme, flash, auto and/or scene modes, white balance, zoom, image focus, ISO sensitivity, shutter speed, image color parameters, etc. Furthermore, the image section, as well as the distance and orientation between the camera and the object or area may be standardized. For example, the image size may be 4:3 with 3648 x 2736 pixel; the image format may be raw, the image color scheme may be neutral, the internal flash may be deactivated, the external flash may be activated, the mode may be set to auto, the white balance may be set to auto, the zoom may be deactivated, the image focus may be set to autofocus TTL, the ISO sensitivity may be set to a defined value (e.g. a value between 200 and 400), the shutter speed may be set to auto, and/or the image color parameter is set to neutral. In one example, the ISO sensitivity is 200. In general, the ISO sensitivity may be as low as possible. In one example, the distance between the camera and the object or area is at least 2 m. In general, the distance between the camera and the object or area should be selected based on the power of the flash, i.e. to ensure that the flash (e.g. the camera-internal flash or the external flash) is able to adequately illuminate the object or area.

[0093] Also, the preparation of the measurement device or imaging device may be standardized, e.g. the method for disinfection of the measurement diaphragm of a spectrophotometer. Also, the pre-treatment of the gross area and/or one or more segment

areas prior to obtaining the image may be standardized, e.g. covering, uncovering, cleaning, drying and/or disinfection of the gross area and/or one or more segment areas. The measurement or imaging conditions may be further standardized by selecting the same personnel for obtaining the measurements or images, and by properly training said personnel in all standardization conditions.

[0094] In an example, the image represents the gross area.

[0095] The image may also comprise an identification object, such as a patient identification card, a hospital bar code, a QR code or the like.

[0096] In one example, the image is saved in a format that is uncompressed, or lossless or nearly lossless compressed, i.e. comprises minimally processed data from the image sensor of the imaging device (e.g. camera, scanner, etc.). In an example, the image is saved in a Raw format. In another embodiment, the image is saved in a Tif format. The image may be exported, e.g. for further analysis or visualization, in a format other than Raw format. For example, the image may be converted in a format selected from the group consisting of Tif, Png, or other lossless compressed image formats. In one example, the image is saved in a Raw format, first converted into a Tif format, and the Tif format is then converted into an Png format. In one example, the conversion from the Raw format to a format for exportation is a lossless or nearly lossless compression. This can be achieved e.g. by using a suitable Raw converter or graphics software, such as Adobe Photoshop, Corel Paint Shop, Corel Photo Paint, Irfan View, GIMP, Paint.NET, or the like. For pure visualization, the image may also be converted in any other suitable format, such as e.g. Jpeg.

[0097] In order to adjust any potential differences in imaging devices, light exposure, or other variable imaging conditions, the image may comprise a standard reference object, such as a color calibration tool (e.g. a gray card and/or a color card). In one embodiment, the color calibration tool is a QP calibration card, as described for example in EP 1240549, WO2004/028144, and/or PCT/SE2011/050367.

[0098] Accordingly, the data underlying the erythema value, e.g. the L* and a* values, may be normalized to a reference, such as a color calibration tool.

[0099] In one embodiment, the erythema value are normalized based on the maximal values for a* and L*.

[0100] For example, the erythema value may be converted into a relative value compared to the respective maximal value, which is set to 100%, in order to compare several erythema values based on different measurement methods or imaging methods, and/or based on different color depths.

[0101] Optionally, the image may be converted into a false color image in order to visualize and/or analyze skin redness or erythema or ancillary assessed color values. For example, the

image may be converted into a pseudo color image (similar to the color image provided by an infrared camera), e.g. a pseudo gray scale or pseudo red scale image, in which the erythema value is represented in gray scale or red scale (see Figure 2). In said false color image, any "non-red" a* value (or negative a* value; e.g. representing green color in the L*a*b* color space) may be set to a pre-defined value. In an embodiment, any negative a* value is set to the minimal red value. For example, if the color space is the L*a*b* color space and the color depth is 8 bit per channel, then any a* value of 127 or lower may be set to 128. Such false color image may also be used to detect overexposure. Such overexposed images may then be excluded from analysis.

[0102] In one example, the L* value decreases with increasing erythema intensity. In a further embodiment, the a* value increases with increasing erythema intensity. In another example, the L* value decreases and the a* value increases with increasing erythema intensity.

[0103] In an example, only the L* and the a* values are considered. In said embodiment, the erythema or skin color is assessed solely by using the L* and the a* value, and accordingly, the erythema value or skin redness value or redness value is calculated solely based on the L* and the a* value. However, since the a* value of the L*a*b* color space may include negative a* values representing green color, green color may be considered as well in the methods of the present invention. Since in skin or mucosa usually the positive a* values (or red values) prevail over negative a* values (or green values), it is not necessary to exclude any negative a* values because of their insignificant influence on the mean erythema value of the skin or mucosal area. In one embodiment, all a* values are considered, i.e. negative as well as positive a* values. Thus, in one example, any pixels of an image having a negative a* values are included into the calculation of the mean erythema value. However, in another embodiment, only positive a* values are considered. According to said embodiment, any pixels of an image having a negative a* value are excluded from the calculation of the mean erythema value. Any other parameters are disregarded, such as e.g. the values for yellow, blue or any other color. According to said embodiment, the erythema value is calculated exclusively based on the values for brightness (from black to white) and redness (which may include the values for green), e.g. the L* value and the a* value.

[0104] In an example, the erythema value provides a continuous erythema intensity measure without any grading or steps, i.e. not depending on any predefined grades.

[0105] In one example, the methods are repeated at several time-points, e.g. at one or more time-points prior to, during, and/or after treatment, development, and/or amelioration of erythema.

[0106] In particular, the light reflectance of a skin or mucosal area of a subject is measured at one or more time-points prior to, during, and/or after development or progression of erythema, or prior to, during, and/or after amelioration or regression of erythema, or prior to, during, and/or after the period of administration of the pharmaceutical or cosmetic preparation, or prior to, during, and/or after the period of treatment (e.g. a local treatment of the skin or mucosal

area, or a systemic treatment of the subject). The gradient between two or more of said erythema values may be determined, e.g. between two or more subsequent measurements or erythema values, or between two or more measurements or erythema values over treatment or observation time. Accordingly, the erythema value calculated based on a measurement taken prior to any treatment (e.g. radiation) and/or manifestation of erythema may be the baseline erythema value. Any erythema value calculated based on a measurement taken during or after any treatment (e.g. radiation) and/or manifestation of erythema may be a follow-up erythema value.

[0107] The gradient between two or more erythema values may be determined, e.g. between two or more subsequent measurements or erythema values, or between two or more measurements or erythema values over treatment or observation time. An increase of the erythema value between two or more erythema values indicates progression of erythema. No significant change of the erythema value (or no gradient between two or more erythema values) indicates a stable skin or mucosal condition. A decrease of the erythema value between two or more erythema values indicates regression of erythema.

[0108] In an example, the erythema is caused by irradiation and may be selected from the group consisting of radiation induced dermatitis (also called radiation dermatitis, or radiodermatitis) and sunburn.

[0109] In one example, the erythema is caused by chemotherapy with cytotoxic drugs, such as e.g. fluorouracil, capecitabine, cytarabine, sorafenib, or pegylated liposomal doxorubicin (Doxil), or tyrosine kinase inhibitors (e.g. sorafenib and sunitinib). Such erythema may also be called palmar-plantar erythrodysesthesia or hand-foot syndrome.

[0110] In an example, the erythema is caused by drug intake, such as e.g. antibiotics (sulfonamides, penicillins, cefixime), barbituates, lamotrigine, phenytoin (e.g., Dilantin), nonsteroidal anti-inflammatory drugs (NSAIDs); or EGFR inhibitors, for example, anti-EGFR antibody therapy, especially the administration of cetuximab (Erbitux®).

[0111] In an example, the erythema is caused by allergen exposure, such as e.g. various allergens for allergy testing, urushiol (a resin produced by poison ivy and poison oak), penicillin, latex, or wasp, fire ant and bee stings.

[0112] In an example, the erythema is caused by fungal infection, such as e.g. tinea (ringworm), or candida.

[0113] In an example, the erythema is caused by bacterial infection, e.g. with staphylococcus, streptococcus, or by a treponemal disease, such as e.g. syphilis, bejel, pinta and yaws.

[0114] In an example, the erythema is caused by viral infection, and may be selected from the group consisting of shingles, rubella, herpes, hand-foot-mouth disease, enterovirus infection, chickenpox infection, or infection by erythrovirus (erythema infectiosum or fifth disease).

[0115] In an example, the erythema is caused by a skin disease, which may be selected from the group consisting of psoriasis, atopic eczema or atopic dermatitis (neurodermatitis), eczema, or acne.

[0116] In an example, the erythema is caused by a disease affecting internal or external mucosa, e.g. oral, nasal, or intestinal mucosa, and may be selected from the group consisting of inflammatory bowel disease, Morbus Crohn (or Crohn's disease), aphthous stomatitis, conjunctivitis, chronic obstructive pulmonary disease, peptic ulcers, alcohol abuse, and gastritis.

[0117] In an example, the erythema is caused by a somatoform disorder, such as blushing.

[0118] As described above, for a subjective assessment of erythema, e.g. radiodermatitis, validated assessment tools are available, such as the classification system "Common Terminology Criteria for Adverse Effects" (CTCAE, e.g. CTCAE version 4.03), which has been developed by the Radiation Therapy Oncology Group (RTOG) and the National Cancer Institute (NCI).

[0119] According to said CTCAE grading, grade 1 radiodermatitis include faint erythema or dry desquamation, which may be accompanied by pruritus, skin distension, hair loss, and pigment alteration. These skin irritations normally occur a couple of days or up to a couple of weeks after the beginning of radiation treatment. Grade 2 radiodermatitis skin irritations include moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases, and a moderate edema. These skin irritations are often painful and bear an increased risk of infection (Hymes, Strom, & Fife, 2006). In grade 3 radiodermatitis according to said CTCAE grading the area of moist desquamation spreads to areas outside of the skin folds. Haemorrhage from minor trauma and abrasion are often present. Grade 4 radiodermatitis is a life-threatening condition characterized by skin necrosis and ulceration of full thickness dermis. There is a particularly high risk of spontaneous bleeding. These changes are very painful and are characterized by poor healing. Skin grafts may be needed. Grade 5 radiodermatitis according to said CTCAE grading leads to the death of the patient.

[0120] In one example, the erythema is a radiation dermatitis of grade 0, 1, 2, 3, or 4. In one embodiment, the erythema is a radiation dermatitis of grade 0 or higher, 1 or higher, 2 or higher, 3 or higher, or 4 or higher. In one embodiment, the erythema is a radiation dermatitis according to grade 0 to 1. In one embodiment, the erythema is a radiation dermatitis according to grade 0 to 2. In one embodiment, the erythema is a radiation dermatitis according to grade 0 to 3. In one embodiment, the erythema is a radiation dermatitis according to grade 0 to 4.

[0121] In one embodiment, the subject is a human. In one embodiment, the subject is a non-human animal. The non-human animal may be a mammal selected from the group consisting of primates (non-human primates), pigs, rodents, or rabbits. On an example, the subject is a cancer patient who is or will be treated with radiation. In one example, the subject is a breast

cancer patient, who is or will be treated with radiation. The breast cancer patient may have undergone surgery, e.g. breast-preserving surgery. In one embodiment, the subject is a head and neck cancer (HNC) patient who is or will be treated with radiation. The HNC patient may have undergone surgery. The subjects may also be treated with a chemotherapy.

[0122] In one example, the erythema value is calculated based on a measurement or image obtained prior to and/or at the beginning of irradiation. In said example, the erythema value is a baseline erythema value (i.e. the initial or reference erythema value). Irradiation may be treatment with or exposure to x-ray, UV irradiation, and/or solar irradiation. In one example, the erythema caused by irradiation is dermatitis radiation grade 2 or higher according to the CTCAE as described above. In one example, erythema caused by irradiation is characterized by epitheliolysis, desquamation, and/or rash. In one example, erythema caused by irradiation is characterized by initial or minor epitheliolysis, desquamation, and/or rash.

[0123] The calculation of the erythema value prior to or at the beginning of irradiation (baseline erythema value, or initial erythema value), as well as the gradient between the erythema values measured during the initial phase of irradiation according to the present invention allows to predict the risk to develop erythema, the intensity of erythema, and/or the time to occurrence of erythema. Thus, the erythema value provides a prognostic factor in radiation therapy and may be used to assess and/or adapt the dose and/or duration of radiation. Furthermore, the baseline erythema value and/or any follow-up erythema values may be used to assess and/or adapt the dose and/or duration of a treatment and/or prophylaxis, such as the treatment and/or prophylaxis of one or more adverse events of radiation or adverse drug reactions of a treatment. With said methods, it is possible to provide a prognosis of the expected severity of radiation dermatitis, as well as the time until a prophylaxis and/or treatment has to be given.

[0124] As can be seen in the examples of the present invention, the baseline erythema value strongly correlates to the grade as well as to the duration until radiation dermatitis of a certain grade (e.g. grade 2) is developed.

[0125] Accordingly, the methods may be used to objectively predict and assess the grade of erythema, the time to occurrence of a certain grade of erythema, as well as the individual risk of a subject to develop a certain grade of erythema.

[0126] In contrast to the erythema value, the Fitzpatrick Scale (Table 2) did not correlate with the developed grade of radiation dermatitis in the studies underlying the present invention. The Fitzpatrick Scale (also called Fitzpatrick skin typing test or Fitzpatrick phototyping scale) is a numerical classification schema for the color of skin. It was developed in 1975 by Thomas B. Fitzpatrick, a Harvard dermatologist, as a way to classify the response of different types of skin to UV light. It remains a recognized tool for dermatologic research into the color of skin. It measures several components: genetic disposition, reaction to sun exposure and tanning habits.

Table 2: Fitzpatrick Skin Color Scale

The Fitzpatrick Scale:
Type I (scores 0-7) Light, pale white. Always burns, never tans.
Type II (scores 8-16) White; fair. Usually burns, tans with difficulty
Type III (scores 17-24) Medium, white to olive. Sometimes mild burn, gradually tans to olive.
Type IV (scores 25-30) Olive, moderate brown. Rarely burns, tans with ease to a moderate brown.
Type V (scores over 30) Brown, dark brown. Very rarely burns, tans very easily.
Type VI Black, very dark brown to black. Never burns, tans very easily, deeply pigmented.

[0127] In example, the methods may be used independently of the skin type, and even independent from basic skin color. For example, erythema or skin color may be assessed in subjects with similar and/or different basic skin colors. For comparison of subjects with different skin colors (e.g. of different races), reference erythema values or reference gradients between two or more erythema values of reference areas or reference subjects may be generated and the measured erythema values may be compared to said references.

[0128] Moreover, with these methods, it is possible to assess erythema or skin irritations that are characterized by colors other than red or in addition to red, especially white or black. For example, psoriasis is often characterized by white or silver scale with underlying erythema. In another example, erythema may also be characterized by very dark skin irritations, especially if necrosis of keratinocytes occurs, such as e.g. in Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN, also known as "Lyell's syndrome"). Furthermore, the methods of the presentinvention can be used to document and/or assess wounds and wound healing. In general, the methods of the present invention allow an assessment of skin or mucosal color (or erythema) changes between two or more measurements.

[0129] A description of radiotherapy in breast cancer, skin reactions caused by radiotherapy, the visual assessment of erythema by the above referenced CTCAE grading, spectrophotometric methods and analysis can be found e.g. in Haigis 2005 (Kristine Haigis, Inaugural-Dissertation zur Erlangung des medizinschen Doktorgrades der Medizinischen Fakultät der Albert-Ludwigs-Universität Freiburg im Breisgau).

[0130] In another aspect, a software tool for erythema monitoring and analysis by using the methods is provided. A software tool is used computer-based. Thus the method is generally computer-implemented. Accordingly, the above described methods may be integrated into a software platform that runs on a computer or computer-like device. Said software platform may be web based (or cloud based), and may include tools for image generation and data input (e.g. mobile imaging and/or computer imaging, patient identification and/or patient information), data management and data output (e.g. databases and/or statistics), as well as data security (e.g. encryption). For example, mobile devices such as smartphones, tablets, i-

phones, i-Pads etc. may be used for the methods of the present invention.

[0131] The software tool according to the invention may be a mobile application or in another embodiment may integrate into the software platform of a stationary device (e.g. a radiation machine). At any point during the method of the invention, method-relevant data may be transmitted over computer-based networks such as the internet or local area networks or wireless networks, and the method may be continued at a another physical location or locations, such as a web-based or cloud-based server or computer.

[0132] Examples of medical software tools for the documentation and analysis of clinical data are, for example, the Secure Platform for Integrating Clinical Services (SPICS) systems provided by the company RISE (Research Industrial Systems Engineering GmbH), developed by RISE and the Technical University Vienna, e.g. the SPICS SOUL (http://soul-doc.com/) and SPICS VASC (http://vasc-world.com/), as well as the SPICS based W.H.A.T system (referenced above). The software tools of the prior art, especially the W.H.A.T system, as well as the methods for assessing erythema described in the prior art may be improved by using the methods of the present invention, in particular, the calculation of the erythema value or the methodically derived yellowness value.

[0133] In addition to the methods of the present invention, subjective assessment of erythema may be done. Accordingly, the grade of erythema may be clinically assessed by a physician, e.g. according to the CTCAE. The erythema value calculated with the methods of the invention may be compared to the subjectively assessed erythema grade.

[0134] The methods according to the invention, especially the calculation of the erythema value, can be used to assess erythema caused by a treatment or disease, to assess the efficacy of a treatment that may ameliorate erythema, and/or to assess the opacity of a cosmetic preparation. For example, the non-therapeutical methods of the invention may be used for demonstrating the efficacy of a pharmaceutical and/or cosmetic product. Said pharmaceutical product may be intended for the prevention and/or amelioration of erythema. Said cosmetic product may be a non-therapeutic product, e.g. for prevention or amelioration of the appearance of erythema, and/or for covering erythema. Furthermore, the methods of the present invention may be used to identify a subject as prone to erythema caused by irradiation. The methods allow an improvement in erythema management in daily care. Moreover, the calculation of the erythema value, especially the baseline erythema value (i.e. the initial erythema value prior to any treatment, or reference erythema value), may be used for selecting and/or deselecting subjects, e.g. for a treatment, a prophylaxis, or for participation in a clinical trial. For example, the baseline erythema value, as well as any follow-up erythema values, or the gradient between two or more of such erythema values, may be used in the planning and conduction of clinical trials, e.g. as prospective screening parameter to impede dilution of study data by patients at a lower risk of developing radiodermatitis. Moreover, the erythema value may be used to generate standard erythemal curves, standard erythema doses, and/or erythema reference action spectra, e.g. according to the ISO 17166 CIE S 007/E.

[0135] In addition, the methods may be used to assess erythema, e.g. skin toxicities, in an animal model, e.g. in research and pre-clinical development of a pharmaceutical preparation, or in the development of a cosmetic preparation. For example, the methods according to the invention may be used in an acute dose toxicity study and/or in a repeated dose toxicity study. The methods of the invention may also be used to measure the skin irritation potential of a pharmaceutical or cosmetic preparation.

[0136] Furthermore, the baseline erythema value or one or more erythema values calculated based on measurements during the initial phase of irradiation treatment (e.g. during the first week of radiation therapy with one radiation fraction per day), or the gradient between such two or more erythema values may be used to prospectively assess the risk to develop radiation dermatitis, the time until development of radiation dermatitis, and/or the expected severity of radiation dermatitis, as well as the time until a prophylactic intervention has to be taken.

[0137] With these methods, it is possible to re-analyse any data obtained from the measurements, since measurements or images may be analyzed several times, with several methods, and/or at any point in time.
Still another application of the methods is the analysis of meat. Since meat is characterized by different shades of red color, as well as white and dark colors, the methods of the invention, especially the calculation of the redness value according to the formula of the invention, can be used to identify the animal species from which the meat originates, the part of the animal from which the meat origins, the degree of freshness of the meat, as well as its fat content.

[0138] The present method also relates to a computational method for objective assessment and remote monitoring of erythema by using a mobile application software integrated in a software platform of a mobile device further enabling to automate the allocation between a measurement of an area of a subject and obtained erythema value to such subject. The method also provides a novel timesaving and cost efficient technology capable of being linked with any electronic clinical monitoring and service system.

[0139] In particular, the invention also relates to a method for assessing erythema of a subject comprising the steps of using a software application integrated into a software platform of a mobile device for measuring the light reflectance of a skin or mucosal area of the subject, obtaining the L* value and the a* value of said measurement according to the L*a*b* color space, and calculating the erythema value according to the formula $(L^*_{max} - L^*) \times a^*$. Furthermore, the invention relates to a method for assessing the risk of a subject to develop erythema caused by irradiation by calculating the erythema value according to the invention; an according method for predicting the intensity of erythema that a subject develops due to irradiation; an according method for predicting the time until a subject develops erythema caused by irradiation; an according method for analyzing a pharmaceutical or cosmetic preparation or an allergen for its ability to cause erythema in a subject; and to an according method for analyzing a pharmaceutical or cosmetic preparation for its ability to ameliorate the appearance of erythema in a subject. The invention relates further to methods for analyzing

skin color of a subject, in an example for documenting or analyzing wounds or wound healing of a subject, for documenting hematoma grading and hematoma development of a subject and for documentation and objective assessment of moles or lentigine or freckles of a subject, based on the formula $(L^*_{max} - L^*) \times a^*$. In another aspect, the method relates to the method of analyzing meat based on the formula $(L^*_{max} - L^*) \times a^*$. In another embodiment, the invention refers to an equivalently derived method for calculating the yellowness of a subject comprising the steps of using a software application integrated into a software platform of a mobile device, for measuring the light reflectance of a skin or mucosal or conjunctive area of the subject, obtaining the L* value and the b* value of said measurement according to the L*a*b color space, and calculating the yellowness value according to the formula $(L^*_{max} - L^*) \times b^*$; an according method combined with the erythema value can be used for documenting and analyzing icterus or cyanosis of a subject.

[0140] The present invention also provides computational methods for analyzing and monitoring erythema and any other skin color comprising the usage of a mobile application software integrated in a software platform of a mobile device, measuring the light reflectance of a skin or mucosal area, analyzing said measurement and applying a novel formula to calculate the erythema value. The skin redness or erythema value provides an objective, continuous measure for skin redness or erythema over the entire range of intensities. Accordingly, the higher the skin redness erythema value the higher is the intensity of erythema. Further detection of a quick response or a barcode code the developed method allows to automatize the allocation process between a subject and the obtained color values of such a subject. The invented computational method consequently delivers a novel timesaving and cost efficient technology capable of being linked with any electronic clinical monitoring and service system.

[0141] In another aspect, the invention relates to a method wherein the software application integrated into a software platform of a mobile device is used for analyzing a pharmaceutical or cosmetic preparation or an allergen for its ability to cause erythema. In another aspect, the invention relates to a method wherein the software application integrated into a software platform of a mobile device is used for analyzing a pharmaceutical or cosmetic preparation for its ability to ameliorate the appearance of erythema.

[0142] In another example, the light reflectance of a skin or mucosal area of said subject is measured at least once prior therapeutic use of a pharmaceutical or topical use of a cosmetic preparation, and at one or more time-points during the therapeutic use of a pharmaceutical or topical use of a cosmetic, and the erythema values are calculated for each measurement. The term "therapeutic use of said pharmaceutical or topical use of cosmetic preparation" with regard to said aspects refers to one or more time-points within and/or after the period of therapeutic use of the pharmaceutical or topical use of a cosmetic preparation. For example, the light reflectance of a skin or mucosal area of the subject is measured at one or more time-points after single or repeated therapeutic use of the pharmaceutical or topical use of a cosmetic preparation. The light reflectance of a skin or mucosal area of the subject may also be measured at one or more time-points after the period therapeutic use of the pharmaceutical or topical use of the cosmetic preparation, i.e. when the pharmaceutical or cosmetic

preparation is no longer applied. The gradient between two or more of said erythema values may be determined, e.g. between two or more subsequent measurements or erythema values, or between two or more measurements or erythema values over treatment or observation time. An increase of the erythema value between two or more erythema values over application time indicates progression of erythema, i.e. that the pharmaceutical or cosmetic preparation causes erythema, or is not effective in preventing erythema. No significant change of the erythema value between two or more erythema values over application time indicates a stable skin or mucosal condition, i.e. that the pharmaceutical or cosmetic preparation does not cause erythema, is effective in preventing erythema, is not effective in treating erythema, or is not effective in ameliorating the appearance of erythema. A decrease of the erythema value between two or more erythema values over application time indicates regression of erythema, i.e. that the pharmaceutical or cosmetic preparation is effective in treating erythema, or in ameliorating the appearance of erythema.

[0143] In another example, of the sixth aspect, the opacity of a cosmetic product is analyzed. The cosmetic product may be make-up, a foundation, face powder, camouflage, a cover stick, or a concealer. A decrease of the erythema value after topical use the product indicates that the cosmetic product is effective in covering erythema.

[0144] The present invention also relates to a computational method comprising the use of a software application integrating into a software platform of a mobile device, implying that the measurement or image can be obtained by any suitable mobile measurement method or imaging method, such as e.g. spectrophotometry, video, video frame buffer, and/or digital photography.

[0145] In a preferred embodiment of the present invention the measurement is obtained by using a software application integrating into the software platform of a smartphone (e.g. iPhone 4, iPhone 4S, iPhone 5 or higher) or into a tablet computer (e.g. iPad, iPad Air, iPad Retina or higher)

[0146] In an advantageous example, the measurement may be obtained by using a software application integrating into a software platform of a smartphone with Kinect-like 3D imaging sensors or a wearable computer with an optical head-mounted display (e.g. google glasses).

[0147] The measurement or image may also be obtained by integrating the used software application into the software platform of endoscopic imaging devices. Thus in one example, the measured skin or mucosal area is an internal mucosal area and the light reflectance is measured by endoscopic methods. For example, the methods may be used to diagnose and monitor diseases affecting internal mucosa and their treatment, such as e.g. Morbus Crohn.

[0148] In a preferred embodiment the method further includes a computational step wherein the software application integrated in a mobile software platform automatically detects a barcode or a quick response code or a near field tag allowing automated allocation of a subject ID and the obtained color values of an analyzed area of this subject.

[0149] In another example, the erythema value may be converted into a relative value compared to the respective maximal value, which is set to 100%, in order to compare several erythema values based on different measurement methods or imaging methods, and/or based on different color depths. In a preferred embodiment of the invention, a calculated reddening value (positive a*) is normalized based on the maximal values for L* and a* according to the formula $(L^*_{max} - L^*) \times a^* / (a^*_{max} \times L^*_{max})$.

[0150] In another embodiment a furthermore calculated yellowness value (positive b*) is normalized based on the maximal values for L* and b* according to the formula $(L^*_{max} - L^*) \times b^* / (b^*_{max} \times L^*_{max})$ and in a more advantageous embodiment a furthermore calculated blueness value (negative b*) is normalized based on the maximum value for L* and the minimum value for b* according to the formula $(L^*_{max} - L^*) \times b^* / (b^*_{min} \times L^*_{max})$.

[0151] In case of measured negative a* (green) values a similar technique can be derived according to the formula $(L^*_{max} - L^*) \times b^* / (b^*_{min} \times L^*_{max})$. The provided set of normalization methods may be used for time dependent analysis of erythema in context to any other observed skin color seen during development and therapy of icterus or hematoma or cyanosis of a subject.

[0152] As described earlier, the invention also relates in particular to a computational method which uses a mobile software application integrated in a software platform of a mobile device for erythema assessment and monitoring which applies the derived methods according to the invention. Accordingly, in this context is must be furthermore considered that any of the above described methods according to the present invention may be integrated into a online or cloud based software platform e.g. into a software suite. Said software app, in a preferred embodiment of the invention integrates into a software platform of a mobile device which directly links to a web based (or cloud based) image analysis and monitoring platform further allowing remote erythema assessment and monitoring of a measured area of a subject, and in one embodiment such software app has further access or may include tools for image generation and data input (e.g. mobile imaging and/or computer imaging, automated patient identification and/or allocation of patient information), data management and data output (e.g. databases and/or statistics), as well as data security (e.g. encryption). For example, mobile devices such as smartphones, computer tablets, i-phones (e.g. iPhone 4, iPhone 4S, iPhone 5 or higher), i-Pads (e.g. (e.g. iPad, iPad Air, iPad Retina or higher) etc. may be used for the methods of the present invention.

[0153] In an advantageous example, the measurement may be obtained by using a software application integrating into a software platform of a smartphone with Kinect-like 3D imaging sensors or a wearable computer with an optical head-mounted display (e.g. google glasses). The above embodiments have been disclosed as the best mode presently contemplated by the inventor it has to be noticed, that any of the above described methods connected with the analysis of the erythema value may be combined with a therefrom directly derived

computational method applicable for analyzing the yellowness value of the skin or mucosa or conjunctiva of a subject, e.g. for objective and time resolved quantitative analysis of icterus grading and development of an skin or. The invention is defined in the claims.

Examples

Example 1: Clinical phase 1b study using the methods of the invention

[0154] A clinical phase Ib testing with liposomally formulated recombinant human superoxide dismutase (APN201) delivered positive results in all endpoints analyzed. The pilot study was conducted in a double blind, placebo-controlled fashion and included 20 female breast cancer patients that received radiation therapy (25-28 Rx- fractions; total dose 50.0 Gy - 50.4 Gy) after breast-preserving surgery. In this study, daily topical application of APN201 (rhSOD; 1.6mg/mL) could be proven to be safe and well tolerated with no serious or drug related adverse events reported. Furthermore APN201 showed first signs towards efficacy with regard to pain, intensity of erythema and time to occurrence of grade 2 dermatitis (epitheliolysis).

PATIENT POPULATION

[0155] 20 patients with histologically confirmed early-stage breast cancer, who underwent prior breast-conserving surgery, were included. Further eligibility requirements were: age 18 years or older, Karnofsky performance status ≥ 80% and Bra cup size ≤ D. Patients were excluded if they had bilateral or inflammatory breast cancer, lymphangiosis carcinomatosa, medically significant dermatologic conditions affecting the irradiated area, if the use of other agents with the aim of preventing and/or treating radiation dermatitis was planned, if they took concomitant medications which might exacerbate radiation dermatitis, and if they had a history of previous breast radiation therapy. All patients received whole-breast irradiation using standard opposed medial and lateral tangent fields to a total dose of 50.0 - 50.4 Gy in 25 - 28 irradiation (Rx) fractions. 19 patients completed the study and were analyzed for signs of efficacy.

TREATMENT PLAN AND CLINICAL EVALUATIONS

[0156] For daily topical drug application of APN201/Placebo a split body design was applied by dividing the irradiated region vertically into two symmetric areas. This was carried out in a double blind fashion, starting with fraction one until the end of whole-breast irradiation (Rx fraction 25-28). The gel was applied as a thin film on the breast ≥10 minutes before the radiation therapy (1 mL/ 100 cm^2 of the radiation field size). Furthermore, each day after radiation therapy, both parts of the irradiation area were consecutively covered with

Bepanthen® moisturizing foam spray. Radiation dermatitis was assessed daily, based on the CTCAE v4.03 classification system beginning at baseline before the start of radiotherapy. In order to explore if the objective measurement reflects the clinical assessments of radiodermatitis, both spectrophotometric measurements and digital images of the treatment fields were taken initially at screening and daily from fraction 6 to fraction 25 or 28. The spectrophotometric measurements and digital images were taken on said days prior to the application of the study medication. Digital photographs were taken with the Canon Digital Cam Canon Powershot G12 under stable light conditions and standardized device settings. A color calibration card comprising black, white, three different gray shades, red, green, blue, and yellow has been used for image calibration to improve the comparability of different images. However, the color calibration card was not present in all images. The software that has been used selected the most intensive red value of the image as maximal red value and normalized each other value to said maximal red value. Accordingly, if the card was present in the image, the red color of the card has been selected, if not, the most intense red of the image has been used as maximal red value (e.g. patient's skin, clothing etc). For spectrophotometric measurements, the spectrometer CM-700d (Konica Minolta) was used by applying a measurement diaphragm (Ø 8mm (MAV)), with activated auto-calibration. Single spot measurement was carried out in three standardized regions in the medial and lateral area according to the split body design. The thereby gained data set comprised 2862 single point measurements. Each measurement comprises the complete L*a*b* color space, as approved by the French Commission Internationale de l'Eclairage (CIE). For objective analysis of efficacy we separated the parameters L*, a* and b* for each individual patient (01-20) and mean values were calculated for each fractions (01-28) and measurement regions (plazebo/verum).

FORMULATION AND COMPOSITION

[0157] APN201 is produced and filled according to cGMP. The drug substance (rhSOD) is encapsulated in a proprietary liposomal formulation and mixed in a hydrophilic gel (1.6 mg rhSOD per mL) which consists of 1% Carbopol 981NF matrix (pH 7.4). Na-Methyl-Parabene is added as preservative in line with the use of multi dose containers. The placebo consists of the same concentration of the gel-forming matrix (Carbopol 981NF) like APN201 but contains empty liposomes.

BIOSTATISTICS AND RESULTS

[0158] For all variables assessed, conducted statistical tests are descriptive. Presented data were summarized with respect to demographic and baseline characteristics, safety- and efficacy observations/measurements. Single spot spectrophotometry delivered consecutive L*a*b* values for each patient (n=19) according to fractions (01-25). The parameters L*, a* and b* were analyzed separately and compared between Placebo and Verum treated skin areas (Figure 3). Whereas the means for L* and a* correlated well with the subjective assessment of

radiodermatitis over study time, no correlation was found with respect to the b* value (Figure 3). We combined L* and a* by algorithm (100-L*) x a* which gains a novel objective parameter, the "Erythema Value" (EV) (Figure 4). Final analysis of the time until grade ≥2 development in APN201/Placebo treated skin areas delivered first signs for APN201 efficacy (Figure 5).

RESULTS

[0159] 20 patients were enrolled and randomly assigned to receive APN201 and placebo in the course of fractionated radiotherapy. 50.0 - 50.4 Gy in 25 - 28 fractions (5 x 1.8 - 2 Gy/week).

[0160] All patients were Caucasian female with a median age of 58 years (range, 40-72). In 10 patients the carcinoma was located in the right breast, in 10 patients in the left. The most common skin type according to the Fitzpatrick scale was skin type 3 in 65%, followed by skin type 2 in 20% of the population. One patient had diabetes mellitus type 2 and another had a contact dermatitis to band-aids. One patient discontinued treatment because of her request, thus the intention to treat (ITT) population included 19 patients.

[0161] All efficacy variables were evaluated on the ITT data set. This data set included all patients who had received at least one application of the study medication and provided efficacy data. Only one patient was excluded for efficacy analysis due to a incompliance after visit for fraction 5. Thus the ITT population included 19 patients.

[0162] Inital spectrophotometric analysis of the ITT (n=19) delivered comparable mean values for both split body areas with respect to the investigated parameters, L*, a*, and b*. We observed a trend for a decreasing mean L* and increasing mean a* value over treatment time, unveiling a negative correlation between both objective parameters. This means, the higher the a* value, the more intense is the skin reddening and the lower the L* value the more darker becomes the skin upon irradiation treatment. Both factors correlate with the subjectively assessment of the CTC classification of dermatitis grading 0-2. In contrast, for the b* value, neither a significant change over time, nor a correlation with observed skin reactions could be identified (Figure 3).

[0163] Based on this result we decided to combine the relevant parameters L* and a* by developing the algorithm (100-L*) x a* which resulted in an even more distinct match. The corresponding Box-Blot analysis of this novel parameter in correlation with the clinically assessed grade of radiation dermatitis (grade 0-2) shows a significant increase of the erythema value (EV) mean with higher grading. For the ITT population a EV mean of 435.9 was calculated at the time point of initial diagnose of grade 2 dermatitis which could not be reached until the end of therapy for investigations on the whole population due to the low incident rate of observed grade 2 (5 of 19 patients; 26.3%). No difference in the trend between placebo and verum treated areas could be observed over treatment time in this context. Thus, our applied method provides a novel objective parameter, the erythema value, which allows the objective assessment of erythema and hence connected skin toxicities (Figure 4).

[0164] Furthermore, analysis of the time until grade ≥2 development in APN201/placebo treated skin areas delivered first signs for APN201 efficacy. The mean time (number of irradiation fractions) to grade 2 irritation was 20.5 fractions (range 18-24) with placebo and 23.0 fractions (range, 22-24) with APN201.

[0165] Surprisingly the stratification between grade 0-1 and grade 2 patients unveiled a clear difference in the mean EV and observed curve trends between these subgroups (Figure 5). A nearly 2 fold higher start value in the EV could be observed for patients who developed grade 2 (EV 290) when compared to those with developed grade 0-1 (EV 150). In Figure 5, the erythema values have been normalized to the theoretical maximal possible value. Said maximal value has been determined based on the assumption that in this example, the maximal L*value is 100, and the maximal a*value is 127, thus, the product of both is set to be the theoretical maximal possible value. All erythema values measured are normalized to said value.

[0166] The threshold erythema value for the grade 3 erythema is one exemplary value which has been determined subjectively of another patient not included into the study. The value has been measured at the day the patient was first diagnosed with the grade 3 subjectively by a physician, which was at the day of fraction 26. The patient had the same disease and treatment as the study patients.

[0167] In our study no correlation between the radiation field size (cm^2), or the Fitzpatrick-Scale (1-2 vs. 3-4) and the CTC grade 2 was observed. The EV value at baseline revealed to be the only statistical significant parameter ($p=0.015$) being associated to the development of CTC grade 2. Furthermore, a direct correlation of the EV value prior to the irradiation and the estimated risk (≥75% at EV ≥300) for CTC grade 2 development could be observed.

DISCUSSION

[0168] Based on our observations we suppose the introduction of the novel Erythema Value (EV) parameter which prospectively allows to identify patients with a higher risk for the development of radiation induced skin toxicity of CTC grade ≥ 2. Measuring the patient's individual EV at the start of irradiation might be of high clinical relevance in order to consider a potential prophylactic treatment with an antioxidant, such as the topical application of APN201 carried out in our study. Secondly the EV should be considered as prospective screening parameter to impede dilution of study data by patients at a lower risk of developing radiodermatitis.

Example 2: Overlapping color gradients from black to white and red

[0169] To prove the applicability of our proposed erythema value for remote analysis of obtained images of a subject we generated a redness gradient starting from the darkest red color to the brightest red color by in silico method using a color depth of 8 bit per color chanel (R/G/B). This was achieved by increasing the value of the primary R in the RGB color space from 0 to 255 (8 bit) and then kept constant. On the increasing side of R, the primaries G and B both have always the value 0, on the constant side of R, G and B both have increasing values starting from 0 to 255 by step-size 1, see Figure 6B. The resulting values were converted into the L*a*b* color space and displayed in Figure 6A. The fourth series in Figure 6 shows the corresponding erythema values calculated by the formula ((255 - L*) × a*), divided by 255 to get comparable values in the range from 0 to 255. Figure 7 shows the above described redness gradient including all values of the RGB and L*a*b* color space.

[0170] Furthermore a methodical equivalently derived technique was used to test the applicability of our invention for assessing a yellowness value of a skin or mucosa or conjunctive area of a subject, e.g. for objective and time resolved assessment of icterus disease. We generated a yellowness gradient starting from dark yellow (reflecting the color of the yellowish bilirubin pigment observed in a severe grade of icterus) to the brightest yellow color by in silico method using a color depth of 8 bit per color chanel (R/G/B). This was achieved by increasing the value of the primary R in the RGB color space from 0 to 255 (8 bit) and then kept constant. On the increasing side of R, the primary B has always the value 0. On the constant side of R, B has increasing values starting from 0 to 255 by step-size 1. The primary G increases uniformly from 0-255 starting from 0 at the increasing side of R; see Figure 8B. The resulting values were converted into the L*a*b* color space and displayed in Figure 8A. The fourth series in Figure 8 shows the corresponding erythema values calculated by the formula ((255 - L*) × b*), divided by 255 to get comparable values in the range from 0 to 255. Figure 9 shows the above described yellowness value gradient including all values of the RGB and L*a*b* color space.

DISCUSSION

[0171] In accordance with the visual perception of skin reddening by the human eye our method delivers a broad nearly linear range of the calculated erythema value, proving the technical feasibility of our developed method. Consequently the corresponding methodical steps comprising of obtaining the L* value and the a* value of a measurement according to the L*a*b* color space, and calculating the skin redness value according to the formula (L^*_{max} - L*) × a* were technically converted by generation of a software tool integrating in a cloud based erythema assessment and documentation platform. The software tool is further capable to link to any mobile software application for measuring the light reflectance of a skin or mucosal or conjunctive area of the subject.

[0172] Furthermore as a result a therefrom derived computational method was claimed for obtaining the L* and the b* value and calculating the yellowness value of a subject according to

the formula (L^*_{max} - L*) × a* which may allow to further extend the invention for any other observed color value of a subject, e.g yellowish pigmentation in case of icterus or bluish pigmentation in case of cyanosis or hematoma of a skin or mucosa or conjunctive area of a subject.

[0173] Example 3: Using a software app integrating the invented methods to analyse erythema values of Naevus lenticularis areas in a phase I trial (A) and time dependent changes of analyzed erythema values (B)

[0174] To test the capabilities of our software app which integrates the provided methods of our invention, we obtained images of skin areas of 14 different subjects (m/f) which were generated by earlier described standardized imaging procedures accompanying to a clinical phase I trial. The trial aimed on to objectively assess the efficacy of a pharmaceutical substance for its assumed capability to attenuate the intensity of Lentigo solaris due to bleaching of Naevus lenticularis areas. Therefore a set of 20 single neavi were assessed in 12 individual subjects over a total treatment period of 4 week. Erythema analysis started from taken images at the before the onset of topical skin treatment (visit 1) and were finished on the last day (visit 4) 4 week post start of topical treatment. The used software app comprises several tools allowing standardized image generation and automated assignment of generated imaging data to a subject by recognizing a specific QR code which may be assigned to a subject or to a analyzed area (Naevus) of a subject. By using our app on a software platform of a mobile device (iPhone) gained images were encrypted and uploaded into a cloud based online platform. Said software app can directly link to the web based (cloud based) image analysis and monitoring platform further allowing remote erythema assessment and monitoring of a measured area of a subject. The areas of interest (Neavi or reference skin) were marked using a selection tool integrated in our image documentation and assessment platform. Finally single erythema values of different areas of interest were calculated by the invented computational method according to the formula (L^*_{max} - L*) × a* and calculated values were normalized automatically according to the formula (L^*_{max} - L*) × a* / (a^*_{max} x L^*_{max}) gaining relative erythema values. Such relative erythema values may range from 0 for minimum to 1 for maximum.

DISCUSSION

[0175] As given by the exemplary result in Fig. 10A the application of our developed method integrated in a mobile software application enables remote and objective assessment of erythema values in normal appearing skin areas (reference) versus skin areas marked by lentigo solaris. In accordance with the subjective visual perception of consulted dermatologic experts to interpret taken images surprisingly our invented method could further confirm that topical pharmaceutical treatment of lentigo solaris neavi did not lead to a decrease in the mean intensity of lentigo solaris in our subjects, such could here be proven by time dependent analysis of the skin reddening (erythema) value; see figure 10B.

[0176] While the above embodiments and exemplary analysis results have been disclosed as the best mode presently contemplated by the inventor it has to be noticed, that these provided examples and given exemplary analysis results should not be interpreted as limiting, due to the reason that professional skilled people within the field, once provided with the present method, can substantially extend the scope of potential applications as exemplary given in above specific embodiments.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US8150501B **[0009]** **[0009]**
- KR2003083623 **[0010]**
- US2005030372A1 **[0012]**
- EP1240549A **[0097]**
- WO2004028144A **[0097]**
- SE2011050367W **[0097]**

Non-patent literature cited in the description

- **FERNANDO IN et al.**Clin Oncol, 1996, vol. 8, 226-233 **[0004]**
- **PINNIX C et al.**Int J Radiat Oncol Biol Phys, 2012, vol. 83, 41089-94 **[0004]**
- **JUNG et al.**Lasers in Surgery and Medicine, 2005, vol. 37, 186-191 **[0009]**
- **JUNG et al.**Lasers in Surgery and Medicine, 2004, vol. 34, 174-181 **[0009]**
- **T. WILDM. PRINZN. FORTNERW. KROISK. SAHORAS. STREMITZERT. HOELZENBEIN**Digital measurement and analysis of wounds based on colour segmentationEuropean Surgery, 2008, vol. 40, 15-10 **[0011]**
- **S. STREMITZERT. WILD**Digitale Wundanalyse mit W.H.A.T. (Wound Healing Analyzing Tool): Manual der Wundheilung2007000015-22 **[0011]**
- **NISCHEK et al.**IEEE Transactions on Medical Imaging, 1997, vol. 16, 6 **[0012]**
- **HIROTSUGUT**he Journal of Medical Investigation, 1998, vol. 44, 121-126 **[0012]**

- **H.** T**AKIWAKI**Measurement of skin color: practical application and theoretical considerationsThe journal of medical investigation: JMI, 1998, 121-126 [0014]
- **A. CHARDON et al.**Skin colour typology and suntanning pathwaysINTERNATIONAL JOURNAL OF COSMETIC SCIENCE, 1991, vol. 13, 4191-208 [0015]

PATENTKRAV

1. Computer-baseret fremgangsmåde til vurdering af erythema ved et subjekt, omfattende følgende trin:

- måling af lysreflektansen for et hudområde eller slimhindeområde eller bindehindeområde på subjektet; og
- tilvejebringelse af L*-værdien og a*-værdien for den nævnte måling i overensstemmelse med L*a*b*-farverummet; og
- beregning af erythema-værdien i overensstemmelse med formlen

$$(L^*_{max} - L^*) \times a^*.$$

2. Fremgangsmåde ifølge krav 1 til anvendelse ved analyse af et farmaceutisk eller kosmetisk præparat eller et allergen med hensyn til dettes evne til at forårsage erythema eller til anvendelse ved analyse af et farmaceutisk eller kosmetisk præparat med hensyn til dettes evne til at formindske forekomsten af erythema, med den forudsætning, at fremgangsmåden ikke omfatter en behandling ved terapi.

3. Computer-baseret fremgangsmåde ifølge krav 1 til at analysere hudfarve på et subjekt, som yderligere omfatter

- tilvejebringelse af L*-værdien og b*-værdien for den nævnte måling i overensstemmelse med L*a*b-farverummet; og
- beregning af gul-værdien i overensstemmelse med formlen

$$(L^*_{max} - L^*) \times b^*.$$

4. Fremgangsmåde ifølge krav 1 eller 3, til anvendelse ved dokumentation eller analyse af sår eller sårheling hos et subjekt.

5. Fremgangsmåde ifølge krav 1,

- til vurdering af risikoen for at et subjekt udvikler erythema forårsaget ved bestråling, hvor lysreflektansen måles før bestråling, og hvor den beregnede erythema-værdi er en basislinie erythema-værdi, yderligere omfattende trinnet med at

korrelere basislinie erythema-værdien med risikoen for at subjektet udvikler erythema forårsaget ved bestråling;

- til forudsigelse af intensiteten af erythema, som et subjekt udvikler på grund af bestråling, hvor lysreflektansen måles før bestråling og hvor den beregnede erythema-værdi er en basislinie erythema-værdi, som yderligere omfatter trinnet med at korrelere basislinie erythema-værdien med intensiteten af erythema, som subjektet udvikler på grund af bestråling; eller
- til at forudsige tiden indtil et subjekt udvikler erythema forårsaget ved bestråling, hvor lysreflektansen måles før bestråling og hvor den beregnede erythema-værdi er en basislinie erythema-værdi, som yderligere omfatter trinnet med omvendt korrelering af basislinie erythema-værdien med tiden indtil subjektet udvikler erythema forårsaget af bestråling.

6. Fremgangsmåde ifølge ethvert af de foregående krav, hvor erythema-værdien korreleres til intensiteten af erythema og/eller gradienten imellem to eller flere erythema-værdier korreleres til udviklingen af erythema.

7. Fremgangsmåde ifølge ethvert af de foregående krav, hvor lysreflektansen måles i et andet farverum end L*a*b*-farverummet, og L*-værdien og a*-værdien og b*-værdien i overensstemmelse med L*a*b*-farverummet tilvejebringes ved at konvertere lysreflektansværdierne for den nævnte måling til de tilsvarende værdier i L*a*b*-farverummet.

8. Fremgangsmåde ifølge ethvert af de foregående krav, hvor erythema-værdien sammenlignes med en reference erythema-værdi.

9. Fremgangsmåde ifølge krav 1 til anvendelse ved analyse af lentigo solaris eller lentigo simpleks eller lentigo maligna eller lentigo aestiva for et subjekt.

10. Fremgangsmåde ifølge krav 1 eller 3, til anvendelse ved dokumentering og analyse af hæmatoma graduering og hæmatoma udvikling for huden eller slimhinden eller bindehinden på et subjekt over tiden; eller til anvendelse ved dokumentering og analyse af icterus-graduering og icterus-udvikling på huden eller slimhinden eller bindehinden på et subjekt over tiden; eller til anvendelse ved dokumentering og analyse af graden af cyanose og cyanoseudvikling på huden eller slimhinden på et subjekt over tiden.

11. Fremgangsmåde ifølge ethvert af kravene 1 til 10, hvor måletrinnet/trinnene og/eller tilvejebringelsestrinnet eller trinnene og/eller beregningstrinnet eller trinnene eller enhver kombination deraf, især alle trin, udføres under anvendelse af en mobil indretning; fortrinsvis hvor den mobile indretning er en bærbar computer med et optisk på hovedet monteret display, eller en tablet eller smartphone og/eller fortrinsvis hvor den mobile indretning er forbundet med et klinisk serviceydelsessystem og/eller en cancerbestrålingsmaskine.

12. Fremgangsmåde ifølge krav 1 eller 3, som yderligere omfatter den samtidige måling af en normaliseringsmarkør, som indeholder chromatiske kodeelementer til automatiseret markørgenkendelse og belysningskorrektion for beregnede farveværdier, fortrinsvis
hvor normaliseringsmarkøren er udformet som et klæbemærke eller et klæbeplaster eller poster.

13. Fremgangsmåde ifølge krav 1 eller 3 eller 12, hvor normaliseringen af en målt erythema-værdi udføres i overensstemmelse med formlen

$$(L^*_{max} - L^*) \times a^* / (a^*_{max} \times L^*_{max});$$

eller
hvor normalisering af en målt gul-værdi udføres i overensstemmelse med formlen

$$(L^*_{max} - L^*) \times b^* / (b^*_{max} \times L^*_{max}) .$$

14. Fremgangsmåde ifølge krav 1 eller 3, som yderligere omfatter trinnet med detektering af en stregkode eller en "quick response code" eller en nærfeltmarkør for subjektet for at automatisere allokeringsprocessen imellem et subjekt og de tilvejebragte farveværdier for subjektet.

15. Fremgangsmåde ifølge ethvert af de foregående krav, som yderligere omfatter tilvejebringelse af den målte lysreflektans, fortrinsvis ved transmission via et netværk; fortrinsvis hvor lysreflektansen ikke måles men tilvejebringes på anden måde; og/eller fortrinsvis hvor tilvejebringelsestrinnet/trinnene og/eller beregningstrinnet/trinnene, især

alle de nævnte trin, udføres under anvendelse af netbaserede eller skybaserede processer.

DRAWINGS

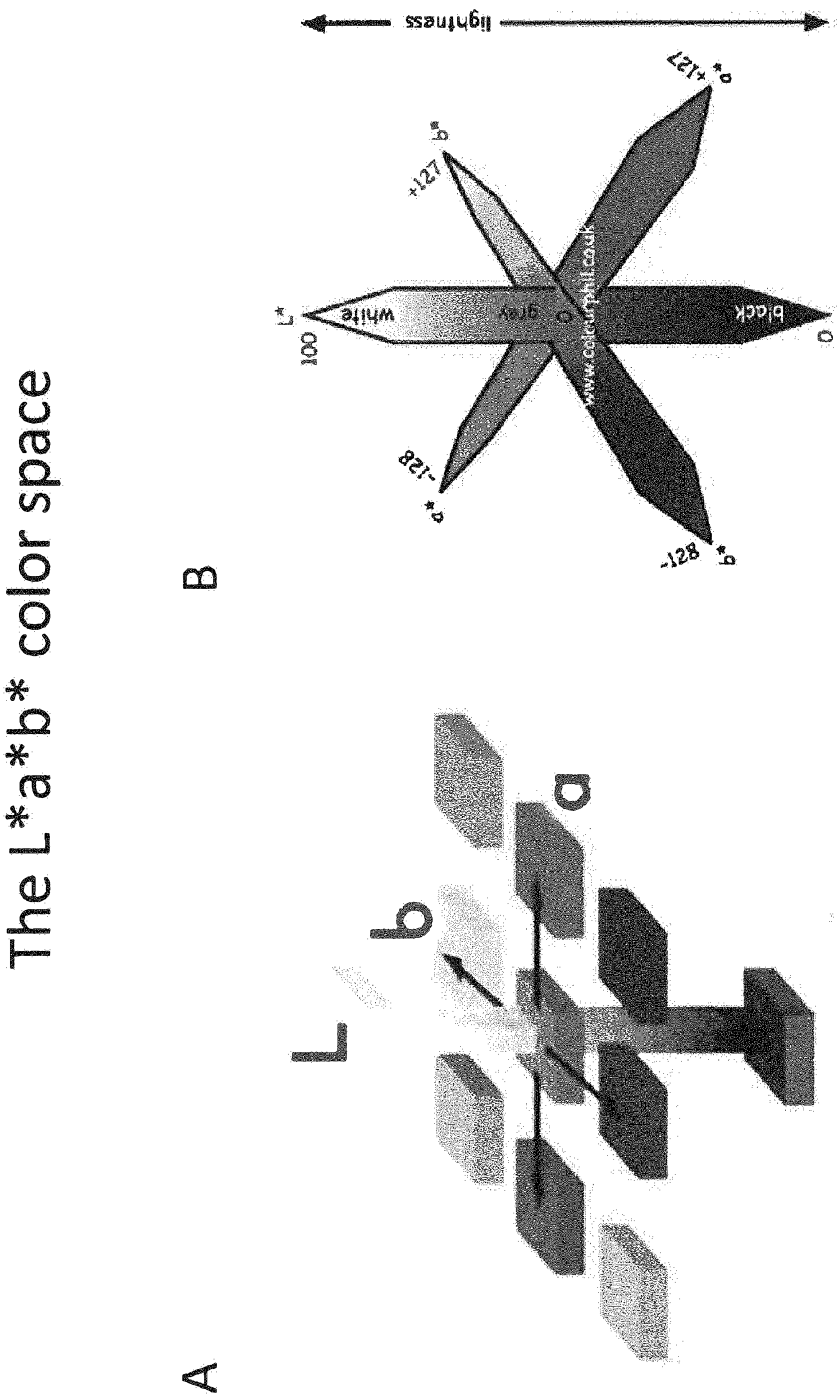
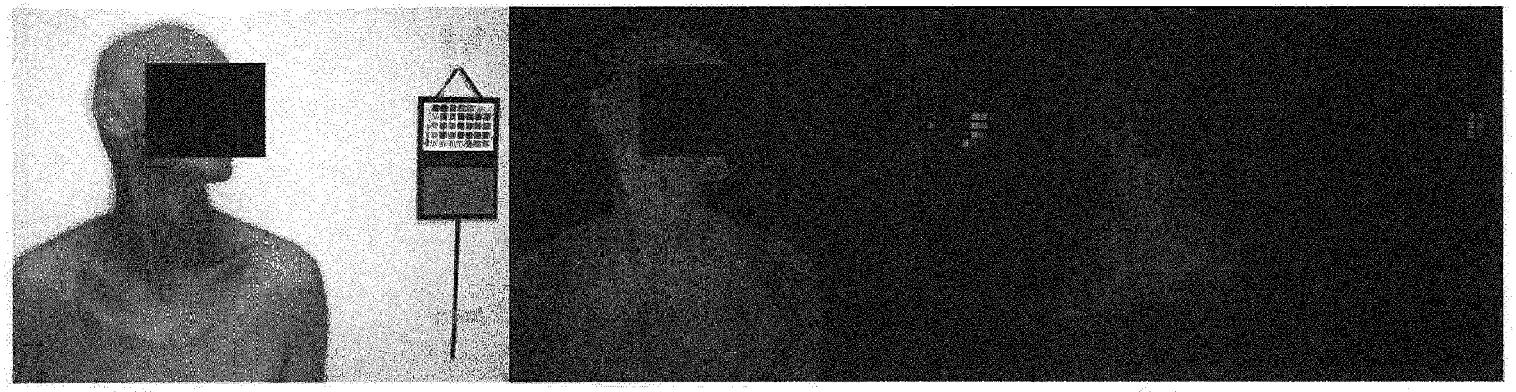


Figure 1



Original a* (100-L)*a

Figure 2

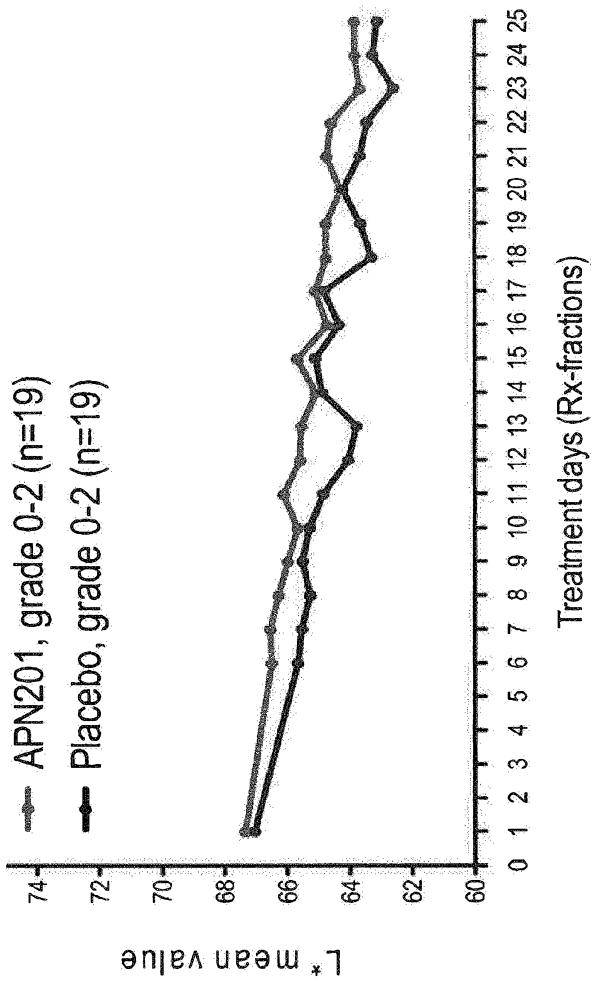

APN201, grade 0-2 (n=19)
Placebo, grade 0-2 (n=19)
L* mean value
74
72
70
68
66
64
62
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Treatment days (Rx-fractions)

Figure 3 A

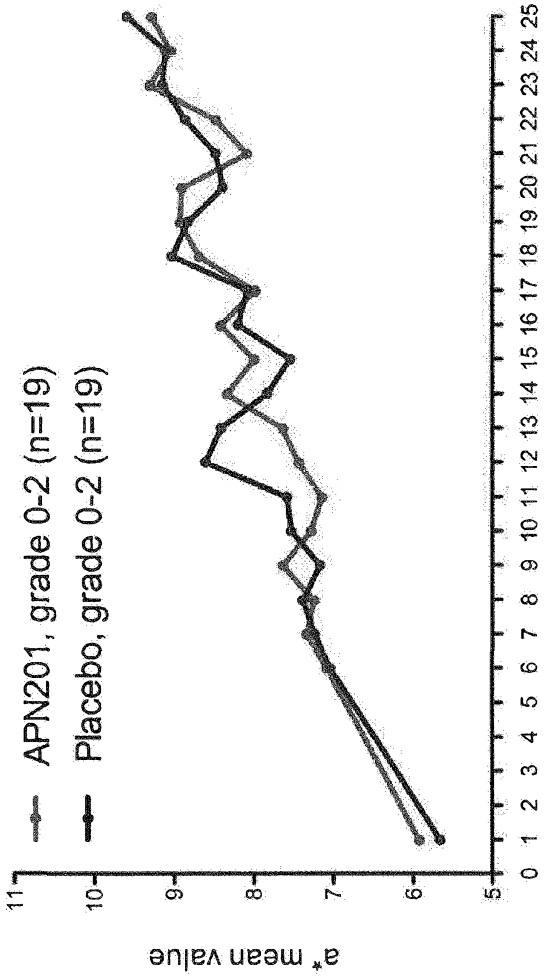

APN201, grade 0-2 (n=19)
Placebo, grade 0-2 (n=19)
a* mean value
11
10
9
8
7
6
5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Treatment days (Rx-fractions)

Figure 3 B

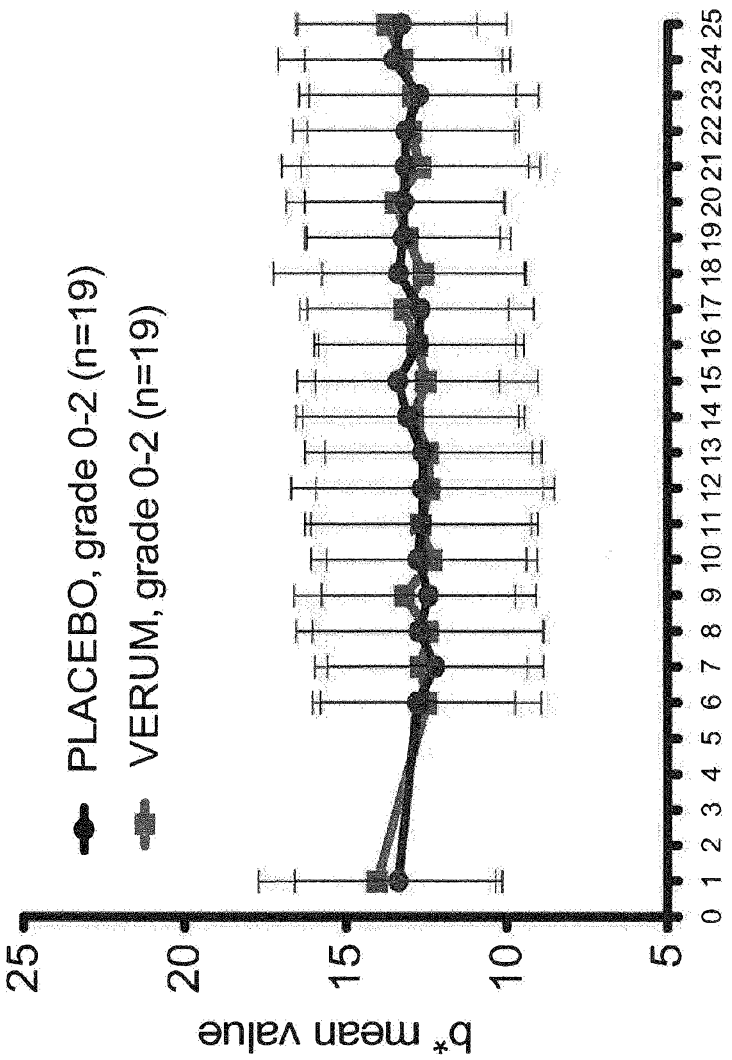

PLACEBO, grade 0-2 (n=19)
VERUM, grade 0-2 (n=19)
b* mean value
25
20
15
10
5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Treatment days (Rx-fractions)

Figure 3 C

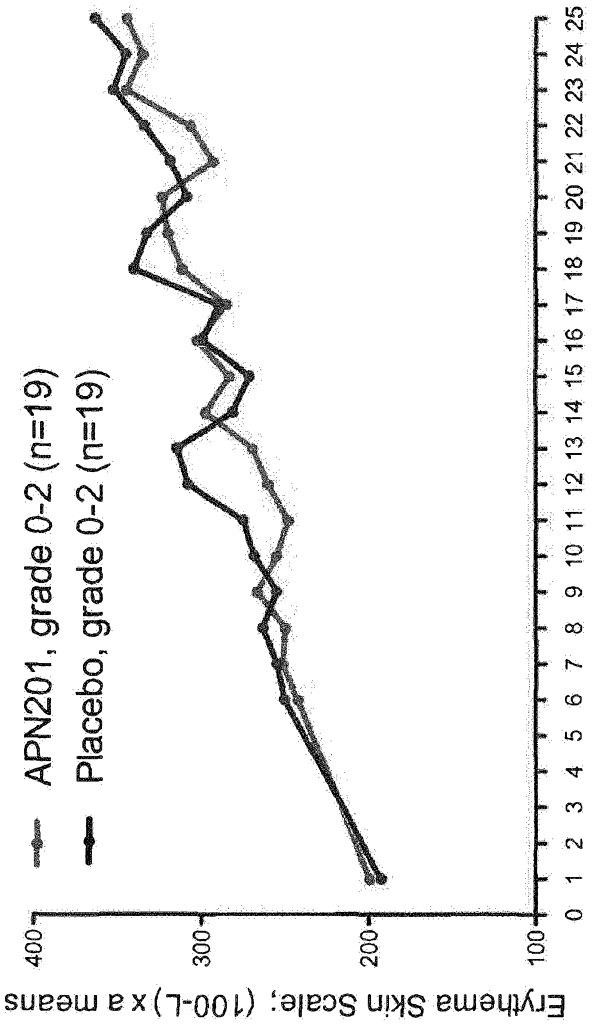

APN201, grade 0-2 (n=19)
Placebo, grade 0-2 (n=19)
Erythema Skin Scale; (100-L) x a means
400
300
200
100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Treatment days (Rx-fractions)

Figure 4 A

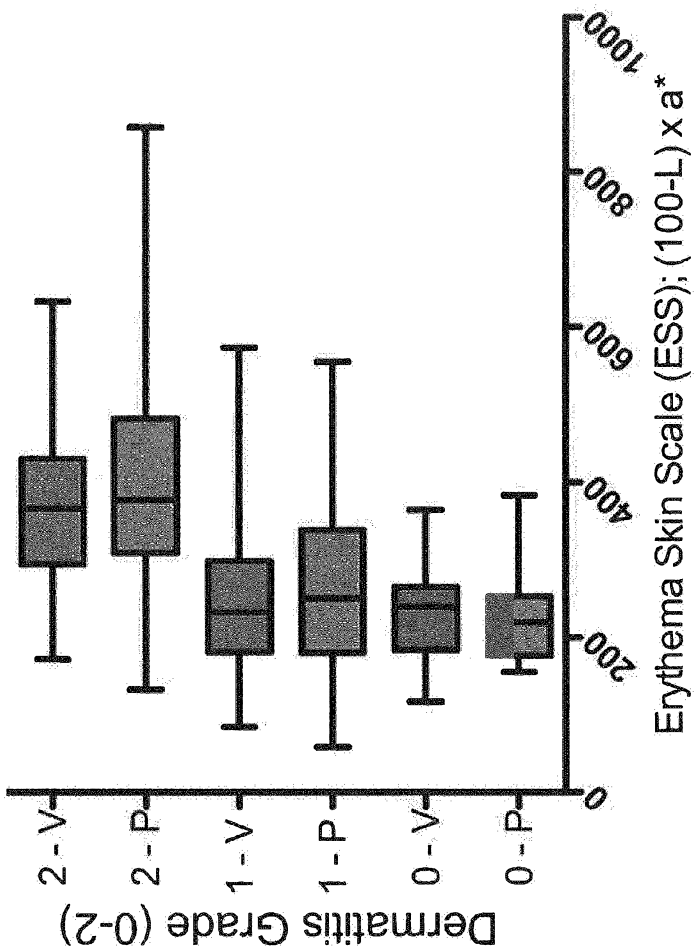
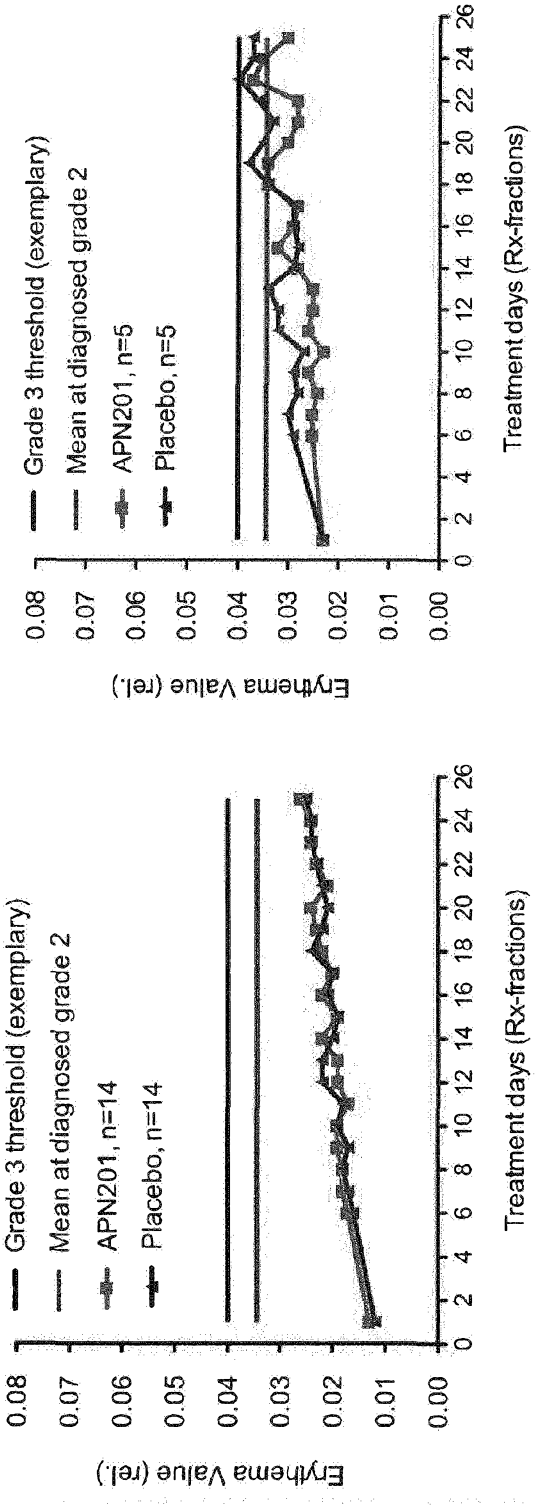
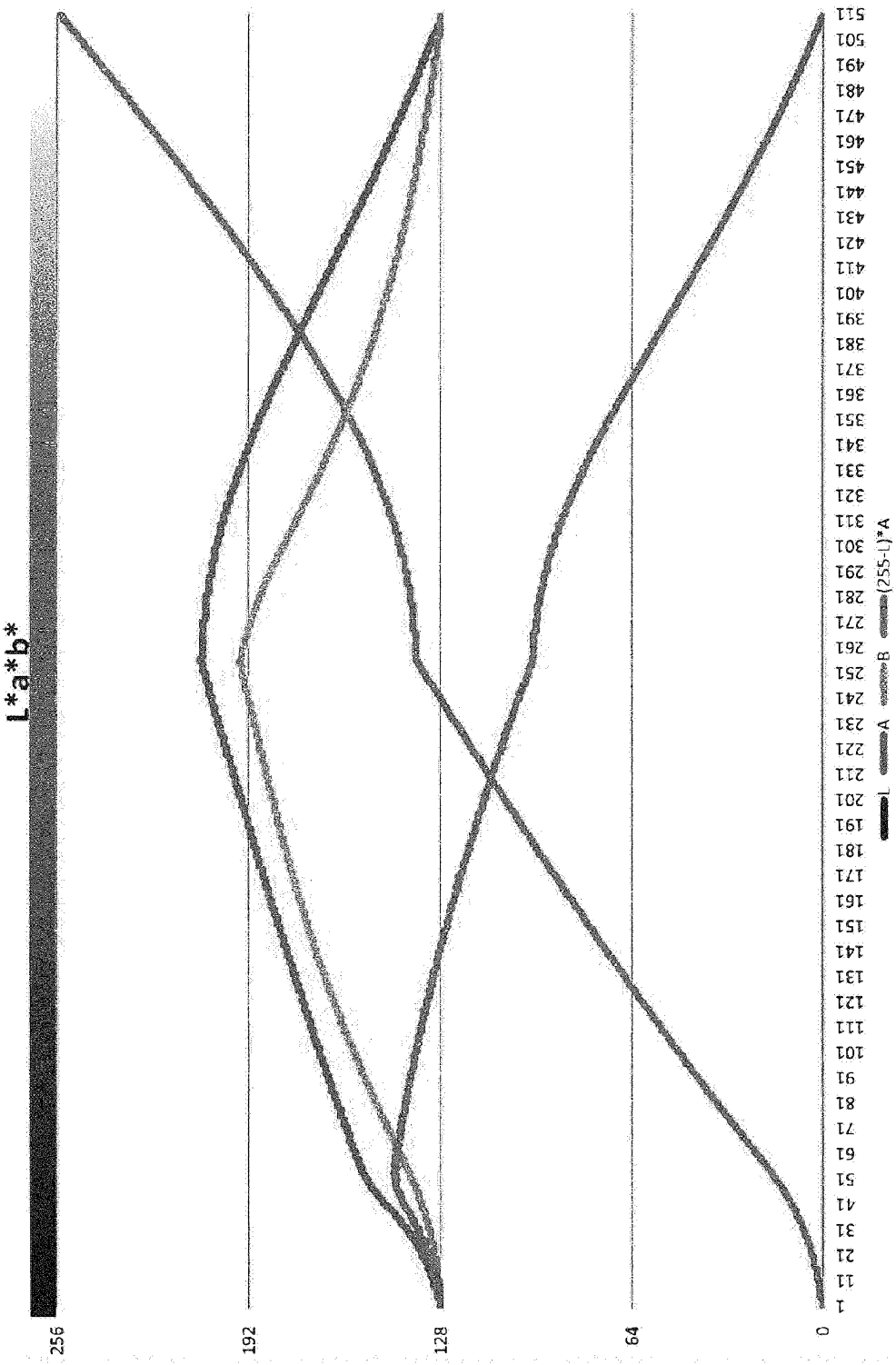

Erythema Skin Scale (ESS); (100-L) x a*
0
200
400
600
800
1000
Dermatitis Grade (0-2)
2 - V
2 - P
1 - V
1 - P
0 - V
0 - P

Figure 4 B


Grade 3 threshold (exemplary)
Mean at diagnosed grade 2
APN201, n=14
Placebo, n=14
Erythema Value (rel.)
Treatment days (Rx-fractions)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24 26

Grade 3 threshold (exemplary)
Mean at diagnosed grade 2
APN201, n=5
Placebo, n=5
Erythema Value (rel.)
Treatment days (Rx-fractions)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24 26

Figure 5


L*a*b*
256
192
128
64
0
1
11
21
31
41
51
61
71
81
91
101
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491
501
511
L
A
B
(255-L)*A

Figure 6 A

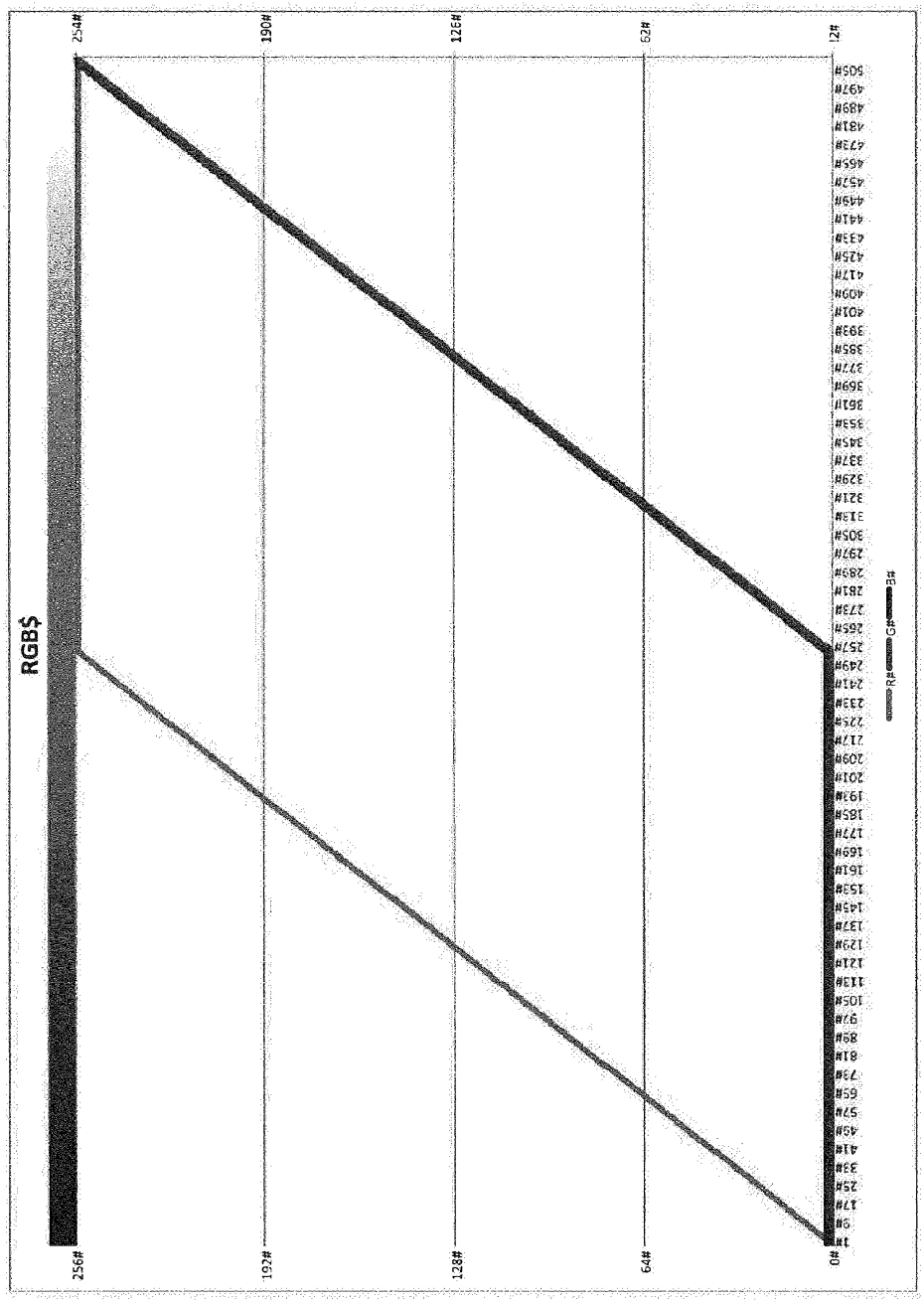

Figure 6 B

R	G	B		L	A	B	(255-L)*A
0	0	0		0	128	128	128
1	0	0		0	128	128	128
2	0	0		0	128	128	128
3	0	0		0	128	128	128
4	0	0		1	129	128	128,494118
5	0	0		1	129	128	128,494118
6	0	0		1	129	128	128,494118
7	0	0		1	129	128	128,494118
8	0	0		1	130	128	129,490196
9	0	0		1	130	128	129,490196
10	0	0		1	130	128	129,490196
11	0	0		2	130	129	128,980392
12	0	0		2	131	129	129,972549
13	0	0		2	131	129	129,972549
14	0	0		2	131	129	129,972549
15	0	0		2	132	129	130,964706
16	0	0		3	132	129	130,447059
17	0	0		3	132	129	130,447059
18	0	0		3	133	129	131,435294
19	0	0		3	133	129	131,435294
20	0	0		3	134	130	132,423529
21	0	0		4	134	130	131,898039
22	0	0		4	134	130	131,898039
23	0	0		4	135	130	132,882353
24	0	0		4	135	130	132,882353
25	0	0		5	136	130	133,333333
26	0	0		5	136	131	133,333333
27	0	0		5	137	131	134,313725
28	0	0		6	138	131	134,752941
29	0	0		6	138	131	134,752941
30	0	0		6	139	131	135,729412
31	0	0		7	139	132	135,184314
32	0	0		7	140	132	136,156863
33	0	0		7	141	132	137,129412
34	0	0		8	141	132	136,576471
35	0	0		8	142	133	137,545098
36	0	0		9	143	133	137,952941
37	0	0		9	143	133	137,952941
38	0	0		9	144	133	138,917647
39	0	0		10	145	134	139,313725
40	0	0		10	146	134	140,27451
41	0	0		11	147	134	140,658824
42	0	0		11	147	135	140,658824
43	0	0		12	148	135	141,035294
44	0	0		12	149	135	141,988235

Figure 7 / 1

45	0	0	[redacted]	13	149	135	141,403922
46	0	0		13	150	136	142,352941
47	0	0		14	151	136	142,709804
48	0	0		14	151	136	142,709804
49	0	0		15	152	137	143,058824
50	0	0		16	152	137	142,462745
51	0	0		16	153	138	143,4
52	0	0		17	153	138	142,8
53	0	0		17	154	138	143,733333
54	0	0		18	154	139	143,129412
55	0	0		19	154	139	142,52549
56	0	0		19	155	140	143,45098
57	0	0		20	155	140	142,843137
58	0	0		21	155	140	142,235294
59	0	0		21	156	141	143,152941
60	0	0		22	156	141	142,541176
61	0	0		23	156	142	141,929412
62	0	0		23	157	142	142,839216
63	0	0		24	157	142	142,223529
64	0	0		25	157	143	141,607843
65	0	0		25	158	143	142,509804
66	0	0		26	158	144	141,890196
67	0	0		27	158	144	141,270588
68	0	0		27	158	144	141,270588
69	0	0		28	159	145	141,541176
70	0	0		29	159	145	140,917647
71	0	0		29	159	146	140,917647
72	0	0		30	160	146	141,176471
73	0	0		31	160	146	140,54902
74	0	0		31	160	147	140,54902
75	0	0		32	161	147	140,796078
76	0	0		33	161	148	140,164706
77	0	0		33	161	148	140,164706
78	0	0		34	161	148	139,533333
79	0	0		35	162	149	139,764706
80	0	0		35	162	149	139,764706
81	0	0		36	162	150	139,129412
82	0	0		37	163	150	139,34902
83	0	0		37	163	150	139,34902
84	0	0		38	163	151	138,709804
85	0	0		39	164	151	138,917647
86	0	0		39	164	151	138,917647
87	0	0		40	164	152	138,27451
88	0	0		40	164	152	138,27451
89	0	0		41	165	153	138,470588
90	0	0		42	165	153	137,823529

Figure 7 / 2

91	0	0	[redacted]	42	165	153	137,823529
92	0	0		43	166	154	138,007843
93	0	0		44	166	154	137,356863
94	0	0		44	166	154	137,356863
95	0	0		45	166	155	136,705882
96	0	0		46	167	155	136,87451
97	0	0		46	167	155	136,87451
98	0	0		47	167	156	136,219608
99	0	0		47	168	156	137,035294
100	0	0		48	168	156	136,376471
101	0	0		49	168	157	135,717647
102	0	0		49	168	157	135,717647
103	0	0		50	169	157	135,862745
104	0	0		51	169	158	135,2
105	0	0		51	169	158	135,2
106	0	0		52	170	159	135,333333
107	0	0		52	170	159	135,333333
108	0	0		53	170	159	134,666667
109	0	0		54	170	160	134
110	0	0		54	171	160	134,788235
111	0	0		55	171	160	134,117647
112	0	0		55	171	161	134,117647
113	0	0		56	171	161	133,447059
114	0	0		57	172	161	133,552941
115	0	0		57	172	161	133,552941
116	0	0		58	172	162	132,878431
117	0	0		58	173	162	133,65098
118	0	0		59	173	162	132,972549
119	0	0		60	173	163	132,294118
120	0	0		60	173	163	132,294118
121	0	0		61	174	163	132,376471
122	0	0		62	174	164	131,694118
123	0	0		62	174	164	131,694118
124	0	0		63	174	164	131,011765
125	0	0		63	175	165	131,764706
126	0	0		64	175	165	131,078431
127	0	0		65	175	165	130,392157
128	0	0		65	176	166	131,137255
129	0	0		66	176	166	130,447059
130	0	0		66	176	166	130,447059
131	0	0		67	176	166	129,756863
132	0	0		67	177	167	130,494118
133	0	0		68	177	167	129,8
134	0	0		69	177	167	129,105882
135	0	0		69	177	168	129,105882
136	0	0		70	178	168	129,137255

Figure 7 / 3

137	0	0		70	178	168	129,137255
138	0	0		71	178	169	128,439216
139	0	0		72	179	169	128,458824
140	0	0		72	179	169	128,458824
141	0	0		73	179	169	127,756863
142	0	0		73	179	170	127,756863
143	0	0		74	180	170	127,764706
144	0	0		75	180	170	127,058824
145	0	0		75	180	170	127,058824
146	0	0		76	180	171	126,352941
147	0	0		76	181	171	127,054902
148	0	0		77	181	171	126,345098
149	0	0		77	181	172	126,345098
150	0	0		78	181	172	125,635294
151	0	0		79	182	172	125,615686
152	0	0		79	182	172	125,615686
153	0	0		80	182	173	124,901961
154	0	0		80	182	173	124,901961
155	0	0		81	183	173	124,870588
156	0	0		81	183	173	124,870588
157	0	0		82	183	174	124,152941
158	0	0		83	184	174	124,109804
159	0	0		83	184	174	124,109804
160	0	0		84	184	174	123,388235
161	0	0		84	184	175	123,388235
162	0	0		85	185	175	123,333333
163	0	0		86	185	175	122,607843
164	0	0		86	185	175	122,607843
165	0	0		87	185	176	121,882353
166	0	0		87	186	176	122,541176
167	0	0		88	186	176	121,811765
168	0	0		88	186	176	121,811765
169	0	0		89	186	177	121,082353
170	0	0		89	187	177	121,733333
171	0	0		90	187	177	121
172	0	0		91	187	177	120,266667
173	0	0		91	187	178	120,266667
174	0	0		92	188	178	120,172549
175	0	0		92	188	178	120,172549
176	0	0		93	188	178	119,435294
177	0	0		93	188	179	119,435294
178	0	0		94	189	179	119,329412
179	0	0		95	189	179	118,588235
180	0	0		95	189	179	118,588235
181	0	0		96	189	179	117,847059
182	0	0		96	190	180	118,470588

Figure 7 / 4

183	0	0		97	190	180	117,72549
184	0	0		97	190	180	117,72549
185	0	0		98	190	180	116,980392
186	0	0		98	191	181	117,596078
187	0	0		99	191	181	116,847059
188	0	0		100	191	181	116,098039
189	0	0		100	191	181	116,098039
190	0	0		101	192	181	115,952941
191	0	0		101	192	182	115,952941
192	0	0		102	192	182	115,2
193	0	0		102	192	182	115,2
194	0	0		103	193	182	115,043137
195	0	0		103	193	182	115,043137
196	0	0		104	193	183	114,286275
197	0	0		105	193	183	113,529412
198	0	0		105	194	183	114,117647
199	0	0		106	194	183	113,356863
200	0	0		106	194	183	113,356863
201	0	0		107	194	184	112,596078
202	0	0		107	195	184	113,176471
203	0	0		108	195	184	112,411765
204	0	0		108	195	184	112,411765
205	0	0		109	195	185	111,647059
206	0	0		110	196	185	111,45098
207	0	0		110	196	185	111,45098
208	0	0		111	196	185	110,682353
209	0	0		111	196	185	110,682353
210	0	0		112	197	186	110,47451
211	0	0		112	197	186	110,47451
212	0	0		113	197	186	109,701961
213	0	0		113	197	186	109,701961
214	0	0		114	198	186	109,482353
215	0	0		114	198	187	109,482353
216	0	0		115	198	187	108,705882
217	0	0		115	198	187	108,705882
218	0	0		116	199	187	108,47451
219	0	0		117	199	187	107,694118
220	0	0		117	199	188	107,694118
221	0	0		118	199	188	106,913725
222	0	0		118	200	188	107,45098
223	0	0		119	200	188	106,666667
224	0	0		119	200	188	106,666667
225	0	0		120	200	189	105,882353
226	0	0		120	201	189	106,411765
227	0	0		121	201	189	105,623529
228	0	0		121	201	189	105,623529

Figure 7 / 5

229	0	0		122	201	189	104,835294
230	0	0		122	202	190	105,356863
231	0	0		123	202	190	104,564706
232	0	0		124	202	190	103,772549
233	0	0		124	202	190	103,772549
234	0	0		125	203	190	103,490196
235	0	0		125	203	191	103,490196
236	0	0		126	203	191	102,694118
237	0	0		126	203	191	102,694118
238	0	0		127	204	191	102,4
239	0	0		127	204	192	102,4
240	0	0		128	204	192	101,6
241	0	0		128	204	192	101,6
242	0	0		129	205	192	101,294118
243	0	0		129	205	192	101,294118
244	0	0		130	205	193	100,490196
245	0	0		130	205	193	100,490196
246	0	0		131	205	193	99,6862745
247	0	0		132	206	193	99,3647059
248	0	0		132	206	193	99,3647059
249	0	0		133	206	194	98,5568627
250	0	0		133	206	194	98,5568627
251	0	0		134	207	194	98,2235294
252	0	0		134	207	194	98,2235294
253	0	0		135	207	194	97,4117647
254	0	0		135	207	195	97,4117647
255	0	0		136	208	195	97,0666667
255	1	1		136	208	194	97,0666667
255	2	2		136	207	194	96,6
255	3	3		136	207	194	96,6
255	4	4		136	207	194	96,6
255	5	5		136	207	194	96,6
255	6	6		136	207	193	96,6
255	7	7		136	207	193	96,6
255	8	8		136	207	193	96,6
255	9	9		136	207	193	96,6
255	10	10		136	207	192	96,6
255	11	11		136	207	192	96,6
255	12	12		137	207	192	95,7882353
255	13	13		137	207	192	95,7882353
255	14	14		137	207	191	95,7882353
255	15	15		137	207	191	95,7882353
255	16	16		137	207	191	95,7882353
255	17	17		137	206	191	95,3254902
255	18	18		137	206	190	95,3254902
255	19	19		137	206	190	95,3254902

Figure 7 / 6

255	20	20		137	206	190	95,3254902
255	21	21		137	206	189	95,3254902
255	22	22		137	206	189	95,3254902
255	23	23		138	206	189	94,5176471
255	24	24		138	206	188	94,5176471
255	25	25		138	206	188	94,5176471
255	26	26		138	206	188	94,5176471
255	27	27		138	205	187	94,0588235
255	28	28		138	205	187	94,0588235
255	29	29		138	205	187	94,0588235
255	30	30		139	205	186	93,254902
255	31	31		139	205	186	93,254902
255	32	32		139	205	186	93,254902
255	33	33		139	205	185	93,254902
255	34	34		139	204	185	92,8
255	35	35		139	204	184	92,8
255	36	36		140	204	184	92
255	37	37		140	204	184	92
255	38	38		140	204	183	92
255	39	39		140	204	183	92
255	40	40		140	203	182	91,5490196
255	41	41		140	203	182	91,5490196
255	42	42		141	203	182	90,7529412
255	43	43		141	203	181	90,7529412
255	44	44		141	203	181	90,7529412
255	45	45		141	203	180	90,7529412
255	46	46		142	202	180	89,5137255
255	47	47		142	202	179	89,5137255
255	48	48		142	202	179	89,5137255
255	49	49		142	202	179	89,5137255
255	50	50		142	201	178	89,0705882
255	51	51		143	201	178	88,2823529
255	52	52		143	201	177	88,2823529
255	53	53		143	201	177	88,2823529
255	54	54		143	201	176	88,2823529
255	55	55		144	200	176	87,0588235
255	56	56		144	200	176	87,0588235
255	57	57		144	200	175	87,0588235
255	58	58		145	200	175	86,2745098
255	59	59		145	199	174	85,8431373
255	60	60		145	199	174	85,8431373
255	61	61		145	199	174	85,8431373
255	62	62		146	199	173	85,0627451
255	63	63		146	198	173	84,6352941
255	64	64		146	198	172	84,6352941
255	65	65		147	198	172	83,8588235

Figure 7 / 7

255	66	66		147	198	171	83,8588235
255	67	67		147	197	171	83,4352941
255	68	68		148	197	171	82,6627451
255	69	69		148	197	170	82,6627451
255	70	70		148	196	170	82,2431373
255	71	71		149	196	169	81,4745098
255	72	72		149	196	169	81,4745098
255	73	73		149	196	169	81,4745098
255	74	74		150	195	168	80,2941176
255	75	75		150	195	168	80,2941176
255	76	76		150	195	167	80,2941176
255	77	77		151	194	167	79,1215686
255	78	78		151	194	167	79,1215686
255	79	79		151	194	166	79,1215686
255	80	80		152	193	166	77,9568627
255	81	81		152	193	166	77,9568627
255	82	82		152	193	165	77,9568627
255	83	83		153	192	165	76,8
255	84	84		153	192	164	76,8
255	85	85		154	192	164	76,0470588
255	86	86		154	191	164	75,6509804
255	87	87		154	191	163	75,6509804
255	88	88		155	191	163	74,9019608
255	89	89		155	190	163	74,5098039
255	90	90		156	190	162	73,7647059
255	91	91		156	190	162	73,7647059
255	92	92		157	189	161	72,6352941
255	93	93		157	189	161	72,6352941
255	94	94		157	189	161	72,6352941
255	95	95		158	188	160	71,5137255
255	96	96		158	188	160	71,5137255
255	97	97		159	188	160	70,7764706
255	98	98		159	187	159	70,4
255	99	99		160	187	159	69,6666667
255	100	100		160	186	159	69,2941176
255	101	101		160	186	158	69,2941176
255	102	102		161	186	158	68,5647059
255	103	103		161	185	158	68,1960784
255	104	104		162	185	157	67,4705882
255	105	105		162	185	157	67,4705882
255	106	106		163	184	157	66,3843137
255	107	107		163	184	156	66,3843137
255	108	108		164	184	156	65,6627451
255	109	109		164	183	156	65,3058824
255	110	110		165	183	155	64,5882353
255	111	111		165	182	155	64,2352941

Figure 7 / 8

255	112	112		166	182	155	63,5215686
255	113	113		166	182	155	63,5215686
255	114	114		167	181	154	62,4627451
255	115	115		167	181	154	62,4627451
255	116	116		168	180	154	61,4117647
255	117	117		168	180	153	61,4117647
255	118	118		169	180	153	60,7058824
255	119	119		169	179	153	60,3686275
255	120	120		170	179	152	59,6666667
255	121	121		170	178	152	59,3333333
255	122	122		171	178	152	58,6352941
255	123	123		171	178	152	58,6352941
255	124	124		172	177	151	57,6117647
255	125	125		172	177	151	57,6117647
255	126	126		173	176	151	56,5960784
255	127	127		173	176	150	56,5960784
255	128	128		174	176	150	55,9058824
255	129	129		174	175	150	55,5882353
255	130	130		175	175	150	54,9019608
255	131	131		176	175	149	54,2156863
255	132	132		176	174	149	53,9058824
255	133	133		177	174	149	53,2235294
255	134	134		177	173	149	52,9176471
255	135	135		178	173	148	52,2392157
255	136	136		178	172	148	51,9372549
255	137	137		179	172	148	51,2627451
255	138	138		179	172	148	51,2627451
255	139	139		180	171	147	50,2941176
255	140	140		181	171	147	49,6235294
255	141	141		181	170	147	49,3333333
255	142	142		182	170	147	48,6666667
255	143	143		182	170	146	48,6666667
255	144	144		183	169	146	47,7176471
255	145	145		183	169	146	47,7176471
255	146	146		184	168	146	46,7764706
255	147	147		185	168	145	46,1176471
255	148	148		185	168	145	46,1176471
255	149	149		186	167	145	45,1882353
255	150	150		186	167	145	45,1882353
255	151	151		187	166	144	44,2666667
255	152	152		188	166	144	43,6156863
255	153	153		188	166	144	43,6156863
255	154	154		189	165	144	42,7058824
255	155	155		189	165	144	42,7058824
255	156	156		190	164	143	41,8039216
255	157	157		190	164	143	41,8039216

Figure 7 / 9

255	158	158		191	164	143	41,1607843
255	159	159		192	163	143	40,2705882
255	160	160		192	163	142	40,2705882
255	161	161		193	162	142	39,3882353
255	162	162		194	162	142	38,7529412
255	163	163		194	162	142	38,7529412
255	164	164		195	161	142	37,8823529
255	165	165		195	161	141	37,8823529
255	166	166		196	160	141	37,0196078
255	167	167		197	160	141	36,3921569
255	168	168		197	160	141	36,3921569
255	169	169		198	159	141	35,5411765
255	170	170		198	159	140	35,5411765
255	171	171		199	158	140	34,6980392
255	172	172		200	158	140	34,0784314
255	173	173		200	158	140	34,0784314
255	174	174		201	157	140	33,2470588
255	175	175		202	157	139	32,6313725
255	176	176		202	156	139	32,4235294
255	177	177		203	156	139	31,8117647
255	178	178		203	156	139	31,8117647
255	179	179		204	155	139	31
255	180	180		205	155	138	30,3921569
255	181	181		205	154	138	30,1960784
255	182	182		206	154	138	29,5921569
255	183	183		207	154	138	28,9882353
255	184	184		207	153	138	28,8
255	185	185		208	153	138	28,2
255	186	186		209	152	137	27,4196078
255	187	187		209	152	137	27,4196078
255	188	188		210	152	137	26,8235294
255	189	189		211	151	137	26,054902
255	190	190		211	151	137	26,054902
255	191	191		212	150	136	25,2941176
255	192	192		212	150	136	25,2941176
255	193	193		213	150	136	24,7058824
255	194	194		214	149	136	23,9568627
255	195	195		214	149	136	23,9568627
255	196	196		215	149	136	23,372549
255	197	197		216	148	135	22,6352941
255	198	198		216	148	135	22,6352941
255	199	199		217	147	135	21,9058824
255	200	200		218	147	135	21,3294118
255	201	201		218	147	135	21,3294118
255	202	202		219	146	135	20,6117647
255	203	203		220	146	135	20,0392157

Figure 7 / 10

255	204	204		220	146	134	20,0392157
255	205	205		221	145	134	19,3333333
255	206	206		222	145	134	18,7647059
255	207	207		222	144	134	18,6352941
255	208	208		223	144	134	18,0705882
255	209	209		224	144	134	17,5058824
255	210	210		224	143	133	17,3843137
255	211	211		225	143	133	16,8235294
255	212	212		226	143	133	16,2627451
255	213	213		226	142	133	16,1490196
255	214	214		227	142	133	15,5921569
255	215	215		228	141	133	14,9294118
255	216	216		228	141	133	14,9294118
255	217	217		229	141	132	14,3764706
255	218	218		230	140	132	13,7254902
255	219	219		230	140	132	13,7254902
255	220	220		231	140	132	13,1764706
255	221	221		232	139	132	12,5372549
255	222	222		232	139	132	12,5372549
255	223	223		233	139	132	11,9921569
255	224	224		234	138	131	11,3647059
255	225	225		234	138	131	11,3647059
255	226	226		235	137	131	10,745098
255	227	227		236	137	131	10,2078431
255	228	228		236	137	131	10,2078431
255	229	229		237	136	131	9,6
255	230	230		238	136	131	9,06666667
255	231	231		238	136	130	9,06666667
255	232	232		239	135	130	8,47058824
255	233	233		240	135	130	7,94117647
255	234	234		241	135	130	7,41176471
255	235	235		241	134	130	7,35686275
255	236	236		242	134	130	6,83137255
255	237	237		243	134	130	6,30588235
255	238	238		243	133	130	6,25882353
255	239	239		244	133	129	5,7372549
255	240	240		245	133	129	5,21568627
255	241	241		245	132	129	5,17647059
255	242	242		246	132	129	4,65882353
255	243	243		247	132	129	4,14117647
255	244	244		247	131	129	4,10980392
255	245	245		248	131	129	3,59607843
255	246	246		249	131	129	3,08235294
255	247	247		249	130	128	3,05882353
255	248	248		250	130	128	2,54901961
255	249	249		251	129	128	2,02352941

Figure 7 / 11

255	250	250		252	129	128	1,51764706
255	251	251		252	129	128	1,51764706
255	252	252		253	128	128	1,00392157
255	253	253		254	128	128	0,50196078
255	254	254		254	128	128	0,50196078
255	255	255		255	128	128	0

Figure 7 / 12

Figure 8 A

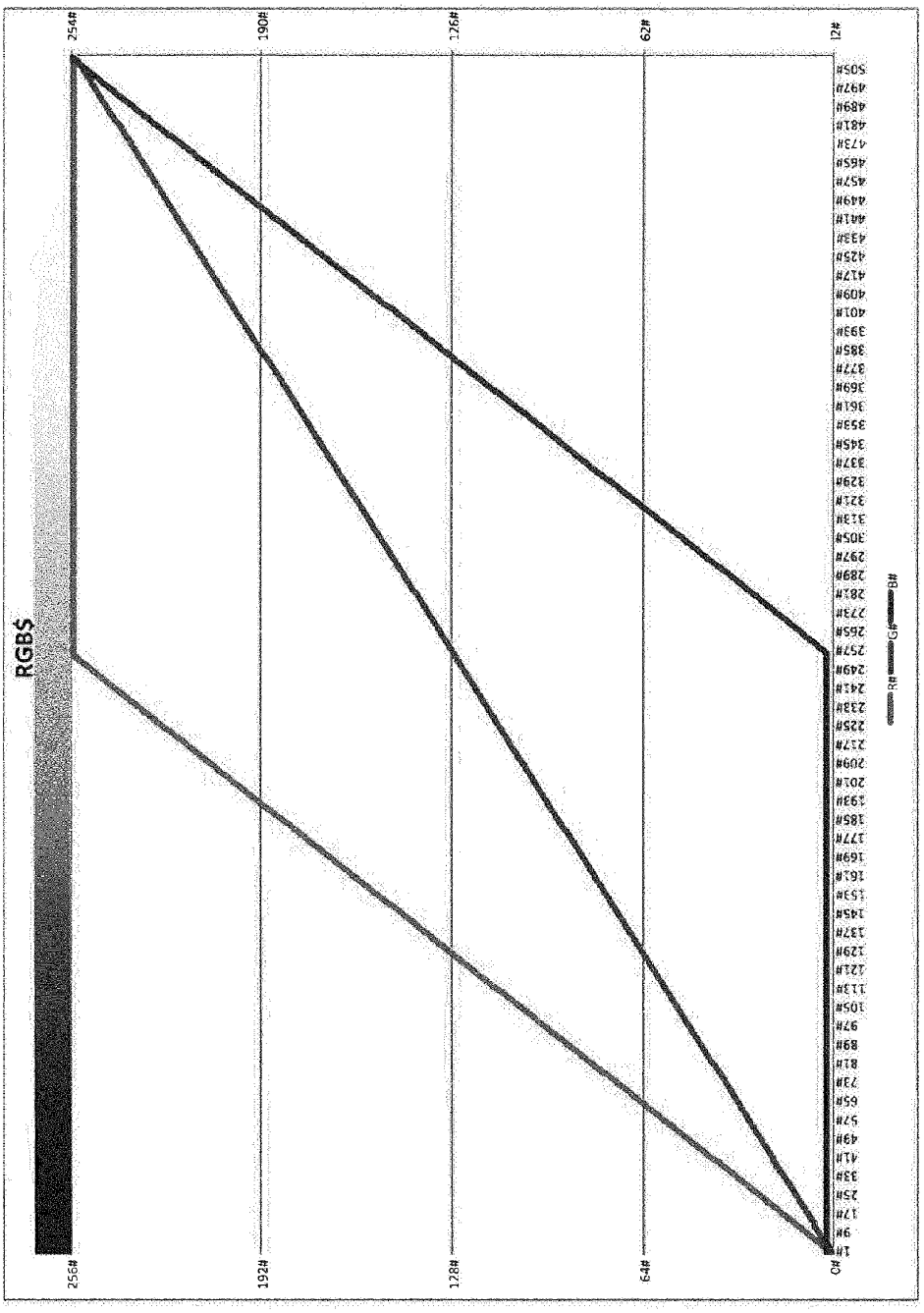

Figure 8B

R	G	B		L	A	B	(255-L)*b
0	0	0		0	0	0	0
1	1	0		8	0	5	4,843137255
2	1	0		10	2	6	5,764705882
3	2	0		19	0	11	10,18039216
4	2	0		21	3	12	11,01176471
5	3	0		28	1	16	14,24313725
6	3	0		29	3	17	15,06666667
7	4	0		35	2	20	17,25490196
8	4	0		37	4	21	17,95294118
9	5	0		41	2	24	20,14117647
10	5	0		43	4	24	19,95294118
11	6	0		47	3	26	21,20784314
12	6	0		48	4	27	21,91764706
13	6	0		49	6	27	21,81176471
14	7	0		52	5	29	23,08627451
15	7	0		53	6	30	23,76470588
16	8	0		57	5	31	24,07058824
17	8	0		57	6	32	24,84705882
18	9	0		61	5	33	25,10588235
19	9	0		61	6	33	25,10588235
20	10	0		64	5	35	26,21568627
21	11	0		67	4	36	26,54117647
22	11	0		68	5	36	26,4
23	12	0		70	5	37	26,84313725
24	12	0		71	6	37	26,69803922
25	13	0		73	5	38	27,12156863
26	13	0		74	6	38	26,97254902
27	14	0		76	5	39	27,37647059
28	14	0		77	6	39	27,22352941
29	15	0		79	5	40	27,60784314
30	15	0		79	6	40	27,60784314
31	16	0		82	5	41	27,81568627
32	16	0		82	6	41	27,81568627
33	17	0		84	6	42	28,16470588
34	17	0		85	6	42	28
35	18	0		86	6	43	28,49803922
36	18	0		87	6	43	28,32941176
37	19	0		89	6	44	28,64313725
38	19	0		89	6	44	28,64313725
39	20	0		91	6	44	28,29803922
40	20	0		91	7	44	28,29803922
41	21	0		93	6	45	28,58823529
42	21	0		94	7	45	28,41176471
43	22	0		95	6	46	28,8627451
44	22	0		96	7	46	28,68235294
45	23	0		97	6	46	28,50196078
46	23	0		98	7	47	28,9372549
47	24	0		99	6	47	28,75294118
48	24	0		100	7	47	28,56862745
49	25	0		101	7	48	28,98823529

Figure 9/1

50	25	0	[redacted]	102	7	48	28,8
51	26	0		103	7	48	28,61176471
52	26	0		104	7	49	29,01568627
53	27	0		105	7	49	28,82352941
54	27	0		105	7	49	28,82352941
55	28	0		107	7	50	29,01960784
56	28	0		107	7	50	29,01960784
57	29	0		109	7	50	28,62745098
58	29	0		109	7	50	28,62745098
59	30	0		110	7	51	29
60	30	0		111	8	51	28,8
61	31	0		112	7	51	28,6
62	31	0		112	8	51	28,6
63	32	0		114	7	52	28,75294118
64	32	0		114	8	52	28,75294118
65	33	0		115	7	52	28,54901961
66	33	0		116	8	53	28,89019608
67	34	0		117	7	53	28,68235294
68	34	0		117	8	53	28,68235294
69	35	0		118	7	53	28,4745098
70	35	0		119	8	54	28,8
71	36	0		120	8	54	28,58823529
72	36	0		120	8	54	28,58823529
73	37	0		121	8	54	28,37647059
74	37	0		122	8	55	28,68627451
75	37	0		122	9	55	28,68627451
76	38	0		123	8	55	28,47058824
77	38	0		123	9	55	28,47058824
78	39	0		124	8	56	28,76862745
79	39	0		125	9	56	28,54901961
80	40	0		126	8	56	28,32941176
81	40	0		126	9	56	28,32941176
82	41	0		127	8	56	28,10980392
83	41	0		127	9	57	28,61176471
84	42	0		129	8	57	28,16470588
85	42	0		129	9	57	28,16470588
86	43	0		130	8	57	27,94117647
87	43	0		130	9	58	28,43137255
88	44	0		131	9	58	28,20392157
89	44	0		131	9	58	28,20392157
90	45	0		133	9	58	27,74901961
91	45	0		133	9	58	27,74901961
92	46	0		134	9	59	27,99607843
93	46	0		134	9	59	27,99607843
94	47	0		135	9	59	27,76470588
95	47	0		135	9	59	27,76470588
96	48	0		136	9	60	28
97	48	0		137	9	60	27,76470588
98	49	0		138	9	60	27,52941176
99	49	0		138	9	60	27,52941176
100	50	0		139	9	60	27,29411765

Figure 9/2

101	50	0	[redacted]	139	9	60	27,29411765
102	51	0		140	9	61	27,50980392
103	51	0		140	9	61	27,50980392
104	52	0		141	9	61	27,27058824
105	52	0		141	9	61	27,27058824
106	53	0		142	9	62	27,4745098
107	53	0		142	9	62	27,4745098
108	54	0		143	9	62	27,23137255
109	54	0		144	9	62	26,98823529
110	55	0		145	9	62	26,74509804
111	55	0		145	10	62	26,74509804
112	56	0		146	9	63	26,92941176
113	56	0		146	10	63	26,92941176
114	57	0		147	9	63	26,68235294
115	57	0		147	10	63	26,68235294
116	58	0		148	9	63	26,43529412
117	58	0		148	10	64	26,85490196
118	59	0		149	9	64	26,60392157
119	59	0		149	10	64	26,60392157
120	60	0		150	9	64	26,35294118
121	60	0		150	10	64	26,35294118
122	61	0		151	10	64	26,10196078
123	61	0		151	10	65	26,50980392
124	62	0		152	10	65	26,25490196
125	62	0		152	10	65	26,25490196
126	63	0		153	10	65	26
127	63	0		153	10	65	26
128	64	0		154	10	66	26,14117647
129	64	0		154	10	66	26,14117647
130	65	0		155	10	66	25,88235294
131	65	0		155	10	66	25,88235294
132	66	0		156	10	66	25,62352941
133	66	0		156	10	66	25,62352941
134	67	0		157	10	67	25,74901961
135	67	0		157	10	67	25,74901961
136	68	0		158	10	67	25,48627451
137	68	0		158	10	67	25,48627451
138	69	0		159	10	67	25,22352941
139	69	0		159	10	67	25,22352941
140	70	0		160	10	68	25,33333333
141	70	0		160	10	68	25,33333333
142	71	0		161	10	68	25,06666667
143	71	0		161	10	68	25,06666667
144	72	0		162	10	68	24,8
145	72	0		162	10	68	24,8
146	73	0		163	10	68	24,53333333
147	73	0		163	10	69	24,89411765
148	74	0		164	10	69	24,62352941
149	74	0		164	10	69	24,62352941
150	75	0		165	10	69	24,35294118
151	75	0		165	10	69	24,35294118

Figure 9/3

152	76	0		166	10	69	24,08235294
153	76	0		166	11	69	24,08235294
154	77	0		167	10	70	24,15686275
155	77	0		167	11	70	24,15686275
156	78	0		167	10	70	24,15686275
157	78	0		168	11	70	23,88235294
158	79	0		168	10	70	23,88235294
159	79	0		168	11	70	23,88235294
160	80	0		169	10	71	23,94509804
161	80	0		169	11	71	23,94509804
162	81	0		170	10	71	23,66666667
163	81	0		170	11	71	23,66666667
164	82	0		171	11	71	23,38823529
165	82	0		171	11	71	23,38823529
166	83	0		172	11	71	23,10980392
167	83	0		172	11	72	23,43529412
168	84	0		173	11	72	23,15294118
169	84	0		173	11	72	23,15294118
170	85	0		173	11	72	23,15294118
171	85	0		174	11	72	22,87058824
172	86	0		174	11	72	22,87058824
173	86	0		174	11	72	22,87058824
174	87	0		175	11	73	22,90196078
175	87	0		175	11	73	22,90196078
176	88	0		176	11	73	22,61568627
177	88	0		176	11	73	22,61568627
178	89	0		177	11	73	22,32941176
179	89	0		177	11	73	22,32941176
180	90	0		178	11	73	22,04313725
181	90	0		178	11	73	22,04313725
182	91	0		178	11	74	22,34509804
183	91	0		179	11	74	22,05490196
184	92	0		179	11	74	22,05490196
185	92	0		179	11	74	22,05490196
186	93	0		180	11	74	21,76470588
187	93	0		180	11	74	21,76470588
188	94	0		181	11	74	21,4745098
189	94	0		181	11	75	21,76470588
190	95	0		182	11	75	21,47058824
191	95	0		182	11	75	21,47058824
192	96	0		182	11	75	21,47058824
193	96	0		182	11	75	21,47058824
194	97	0		183	11	75	21,17647059
195	97	0		183	11	75	21,17647059
196	98	0		184	11	76	21,16078431
197	98	0		184	11	76	21,16078431
198	99	0		185	11	76	20,8627451
199	99	0		185	11	76	20,8627451
200	100	0		185	11	76	20,8627451
201	100	0		186	11	76	20,56470588
202	101	0		186	11	76	20,56470588

Figure 9/4

203	101	0		186	12	76	20,56470588
204	102	0		187	11	77	20,53333333
205	102	0		187	12	77	20,53333333
206	103	0		188	11	77	20,23137255
207	103	0		188	12	77	20,23137255
208	104	0		188	11	77	20,23137255
209	104	0		189	12	77	19,92941176
210	105	0		189	11	77	19,92941176
211	105	0		189	12	77	19,92941176
212	106	0		190	11	78	19,88235294
213	106	0		190	12	78	19,88235294
214	107	0		191	12	78	19,57647059
215	107	0		191	12	78	19,57647059
216	108	0		191	12	78	19,57647059
217	108	0		191	12	78	19,57647059
218	109	0		192	12	78	19,27058824
219	109	0		192	12	78	19,27058824
220	110	0		193	12	79	19,20784314
221	110	0		193	12	79	19,20784314
222	111	0		193	12	79	19,20784314
223	111	0		194	12	79	18,89803922
224	112	0		194	12	79	18,89803922
225	112	0		194	12	79	18,89803922
226	113	0		195	12	79	18,58823529
227	113	0		195	12	79	18,58823529
228	114	0		196	12	79	18,27843137
229	114	0		196	12	80	18,50980392
230	115	0		196	12	80	18,50980392
231	115	0		196	12	80	18,50980392
232	116	0		197	12	80	18,19607843
233	116	0		197	12	80	18,19607843
234	117	0		198	12	80	17,88235294
235	117	0		198	12	80	17,88235294
236	118	0		198	12	80	17,88235294
237	118	0		198	12	80	17,88235294
238	119	0		199	12	81	17,78823529
239	119	0		199	12	81	17,78823529
240	120	0		200	12	81	17,47058824
241	120	0		200	12	81	17,47058824
242	121	0		200	12	81	17,47058824
243	121	0		200	12	81	17,47058824
244	122	0		201	12	81	17,15294118
245	122	0		201	12	81	17,15294118
246	123	0		202	12	81	16,83529412
247	123	0		202	12	82	17,04313725
248	124	0		202	12	82	17,04313725
249	124	0		202	12	82	17,04313725
250	125	0		203	12	82	16,72156863
251	125	0		203	12	82	16,72156863
252	126	0		204	12	82	16,4
253	126	0		204	12	82	16,4

Figure 9/5

254	127	0		204	12	82	16,4
255	127	0		204	12	82	16,4
255	128	0		205	12	83	16,2745098
255	128	1		205	12	81	15,88235294
255	129	2		205	12	80	15,68627451
255	129	3		205	12	79	15,49019608
255	130	4		206	12	78	14,98823529
255	130	5		206	12	77	14,79607843
255	131	6		206	12	76	14,60392157
255	131	7		206	12	75	14,41176471
255	132	8		207	11	74	13,92941176
255	132	9		207	12	73	13,74117647
255	133	10		207	11	72	13,55294118
255	133	11		207	11	71	13,36470588
255	134	12		208	11	70	12,90196078
255	134	13		208	11	69	12,71764706
255	135	14		208	11	69	12,71764706
255	135	15		208	11	68	12,53333333
255	136	16		208	11	67	12,34901961
255	136	17		209	11	66	11,90588235
255	137	18		209	11	65	11,7254902
255	137	19		209	11	65	11,7254902
255	138	20		209	11	64	11,54509804
255	138	21		209	11	63	11,36470588
255	139	22		210	11	63	11,11764706
255	139	23		210	11	62	10,94117647
255	140	24		210	10	61	10,76470588
255	140	25		210	11	60	10,58823529
255	141	26		211	10	60	10,35294118
255	141	27		211	10	59	10,18039216
255	142	28		211	10	59	10,18039216
255	142	29		211	10	58	10,00784314
255	143	30		212	10	57	9,611764706
255	143	31		212	10	57	9,611764706
255	144	32		212	10	56	9,443137255
255	144	33		212	10	56	9,443137255
255	145	34		213	10	55	9,058823529
255	145	35		213	10	54	8,894117647
255	146	36		213	10	54	8,894117647
255	146	37		213	10	53	8,729411765
255	147	38		214	10	53	8,521568627
255	147	39		214	10	52	8,360784314
255	148	40		214	9	52	8,360784314
255	148	41		214	10	51	8,2
255	149	42		214	9	51	8,2
255	149	43		214	9	50	8,039215686
255	150	44		215	9	50	7,843137255
255	150	45		215	9	49	7,68627451
255	151	46		215	9	49	7,68627451
255	151	47		215	9	48	7,529411765
255	152	48		216	9	48	7,341176471

Figure 9/6

255	152	49		216	9	47	7,188235294
255	153	50		216	9	47	7,188235294
255	153	51		216	9	46	7,035294118
255	154	52		217	9	46	6,854901961
255	154	53		217	9	46	6,854901961
255	155	54		217	9	45	6,705882353
255	155	55		217	9	45	6,705882353
255	156	56		218	9	44	6,384313725
255	156	57		218	9	44	6,384313725
255	157	58		218	8	44	6,384313725
255	157	59		218	9	43	6,239215686
255	158	60		218	8	43	6,239215686
255	158	61		218	8	42	6,094117647
255	159	62		219	8	42	5,929411765
255	159	63		219	8	41	5,788235294
255	160	64		219	8	41	5,788235294
255	160	65		219	8	41	5,788235294
255	161	66		220	8	40	5,490196078
255	161	67		220	8	40	5,490196078
255	162	68		220	8	40	5,490196078
255	162	69		220	8	39	5,352941176
255	163	70		221	8	39	5,2
255	163	71		221	8	38	5,066666667
255	164	72		221	8	38	5,066666667
255	164	73		221	8	38	5,066666667
255	165	74		221	8	37	4,933333333
255	165	75		221	8	37	4,933333333
255	166	76		222	7	37	4,788235294
255	166	77		222	8	36	4,658823529
255	167	78		222	7	36	4,658823529
255	167	79		222	7	36	4,658823529
255	168	80		223	7	35	4,392156863
255	168	81		223	7	35	4,392156863
255	169	82		223	7	35	4,392156863
255	169	83		223	7	34	4,266666667
255	170	84		223	7	34	4,266666667
255	170	85		224	7	34	4,133333333
255	171	86		224	7	33	4,011764706
255	171	87		224	7	33	4,011764706
255	172	88		224	7	33	4,011764706
255	172	89		224	7	32	3,890196078
255	173	90		225	7	32	3,764705882
255	173	91		225	7	32	3,764705882
255	174	92		225	7	32	3,764705882
255	174	93		225	7	31	3,647058824
255	175	94		226	6	31	3,525490196
255	175	95		226	7	31	3,525490196
255	175	96		226	7	30	3,411764706
255	176	97		226	6	30	3,411764706
255	176	98		226	7	30	3,411764706
255	177	99		226	6	29	3,298039216

Figure 9/7

255	177	100		226	6	29	3,298039216
255	178	101		227	6	29	3,184313725
255	178	102		227	6	28	3,074509804
255	179	103		227	6	28	3,074509804
255	179	104		227	6	28	3,074509804
255	180	105		228	6	28	2,964705882
255	180	106		228	6	27	2,858823529
255	181	107		228	6	27	2,858823529
255	181	108		228	6	27	2,858823529
255	182	109		228	6	27	2,858823529
255	182	110		228	6	26	2,752941176
255	183	111		229	6	26	2,650980392
255	183	112		229	6	26	2,650980392
255	184	113		229	6	26	2,650980392
255	184	114		229	6	25	2,549019608
255	185	115		230	6	25	2,450980392
255	185	116		230	6	25	2,450980392
255	186	117		230	6	25	2,450980392
255	186	118		230	6	24	2,352941176
255	187	119		230	5	24	2,352941176
255	187	120		230	6	24	2,352941176
255	188	121		231	5	24	2,258823529
255	188	122		231	5	23	2,164705882
255	189	123		231	5	23	2,164705882
255	189	124		231	5	23	2,164705882
255	190	125		232	5	23	2,074509804
255	190	126		232	5	22	1,984313725
255	191	127		232	5	22	1,984313725
255	191	128		232	5	22	1,984313725
255	192	129		232	5	22	1,984313725
255	192	130		232	5	21	1,894117647
255	193	131		233	5	21	1,811764706
255	193	132		233	5	21	1,811764706
255	194	133		233	5	21	1,811764706
255	194	134		233	5	20	1,725490196
255	195	135		234	5	20	1,647058824
255	195	136		234	5	20	1,647058824
255	196	137		234	5	20	1,647058824
255	196	138		234	5	20	1,647058824
255	197	139		234	5	19	1,564705882
255	197	140		234	5	19	1,564705882
255	198	141		235	4	19	1,490196078
255	198	142		235	5	19	1,490196078
255	199	143		235	4	19	1,490196078
255	199	144		235	4	18	1,411764706
255	200	145		235	4	18	1,411764706
255	200	146		235	4	18	1,411764706
255	201	147		236	4	18	1,341176471
255	201	148		236	4	17	1,266666667
255	202	149		236	4	17	1,266666667
255	202	150		236	4	17	1,266666667

Figure 9/8

255	203	151	237	4	17	1,2
255	203	152	237	4	17	1,2
255	204	153	237	4	16	1,129411765
255	204	154	237	4	16	1,129411765
255	205	155	237	4	16	1,129411765
255	205	156	237	4	16	1,129411765
255	206	157	238	4	16	1,066666667
255	206	158	238	4	15	1
255	207	159	238	4	15	1
255	207	160	238	4	15	1
255	208	161	238	4	15	1
255	208	162	238	4	15	1
255	209	163	239	3	14	0,878431373
255	209	164	239	4	14	0,878431373
255	210	165	239	3	14	0,878431373
255	210	166	239	3	14	0,878431373
255	211	167	240	3	14	0,823529412
255	211	168	240	3	13	0,764705882
255	212	169	240	3	13	0,764705882
255	212	170	240	3	13	0,764705882
255	213	171	240	3	13	0,764705882
255	213	172	240	3	13	0,764705882
255	214	173	241	3	13	0,71372549
255	214	174	241	3	12	0,658823529
255	215	175	241	3	12	0,658823529
255	215	176	241	3	12	0,658823529
255	216	177	241	3	12	0,658823529
255	216	178	241	3	12	0,658823529
255	217	179	242	3	12	0,611764706
255	217	180	242	3	11	0,560784314
255	218	181	242	3	11	0,560784314
255	218	182	242	3	11	0,560784314
255	219	183	243	3	11	0,517647059
255	219	184	243	3	11	0,517647059
255	220	185	243	3	10	0,470588235
255	220	186	243	3	10	0,470588235
255	221	187	243	2	10	0,470588235
255	221	188	243	3	10	0,470588235
255	222	189	244	2	10	0,431372549
255	222	190	244	2	10	0,431372549
255	223	191	244	2	9	0,388235294
255	223	192	244	2	9	0,388235294
255	224	193	244	2	9	0,388235294
255	224	194	244	2	9	0,388235294
255	225	195	245	2	9	0,352941176
255	225	196	245	2	9	0,352941176
255	226	197	245	2	8	0,31372549
255	226	198	245	2	8	0,31372549
255	227	199	245	2	8	0,31372549
255	227	200	245	2	8	0,31372549
255	228	201	246	2	8	0,282352941

Figure 9/9

255	228	202	246	2	8	0,282352941
255	229	203	246	2	7	0,247058824
255	229	204	246	2	7	0,247058824
255	230	205	246	2	7	0,247058824
255	230	206	246	2	7	0,247058824
255	231	207	247	2	7	0,219607843
255	231	208	247	2	7	0,219607843
255	232	209	247	2	7	0,219607843
255	232	210	247	2	6	0,188235294
255	233	211	247	2	6	0,188235294
255	233	212	248	2	6	0,164705882
255	234	213	248	1	6	0,164705882
255	234	214	248	2	6	0,164705882
255	235	215	248	1	6	0,164705882
255	235	216	248	2	5	0,137254902
255	236	217	249	1	5	0,117647059
255	236	218	249	1	5	0,117647059
255	237	219	249	1	5	0,117647059
255	237	220	249	1	5	0,117647059
255	238	221	249	1	5	0,117647059
255	238	222	249	1	4	0,094117647
255	239	223	250	1	4	0,078431373
255	239	224	250	1	4	0,078431373
255	240	225	250	1	4	0,078431373
255	240	226	250	1	4	0,078431373
255	241	227	250	1	4	0,078431373
255	241	228	250	1	4	0,078431373
255	242	229	251	1	4	0,062745098
255	242	230	251	1	3	0,047058824
255	243	231	251	1	3	0,047058824
255	243	232	251	1	3	0,047058824
255	244	233	251	1	3	0,047058824
255	244	234	251	1	3	0,047058824
255	245	235	252	1	3	0,035294118
255	245	236	252	1	2	0,023529412
255	246	237	252	1	2	0,023529412
255	246	238	252	1	2	0,023529412
255	247	239	252	1	2	0,023529412
255	247	240	252	1	2	0,023529412
255	248	241	253	0	2	0,015686275
255	248	242	253	1	2	0,015686275
255	249	243	253	0	2	0,015686275
255	249	244	253	0	1	0,007843137
255	250	245	253	0	1	0,007843137
255	250	246	253	0	1	0,007843137
255	251	247	254	0	1	0,003921569
255	251	248	254	0	1	0,003921569
255	252	249	254	0	1	0,003921569
255	252	250	254	0	1	0,003921569
255	253	251	254	0	1	0,003921569
255	253	252	254	0	0	0

Figure 9/10

255	254	253	255 0 0	0
255	254	254	255 0 0	0
255	255	255	255 0 0	0

Figure 9/11

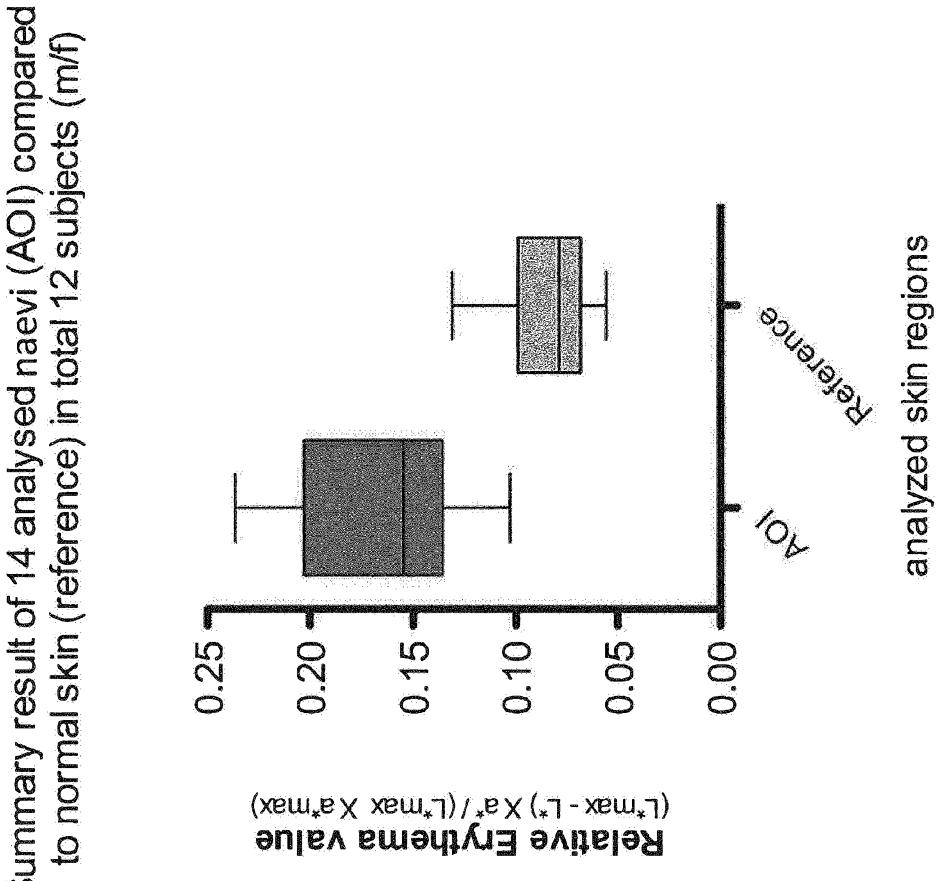
Summary result of 14 analysed naevi (AOI) compared to normal skin (reference) in total 12 subjects (m/f)
Relative Erythema value
(L*max - L*) X a* / (L*max X a*max)
0.25
0.20
0.15
0.10
0.05
0.00
AOI
Reference
analyzed skin regions

Figure 10 A

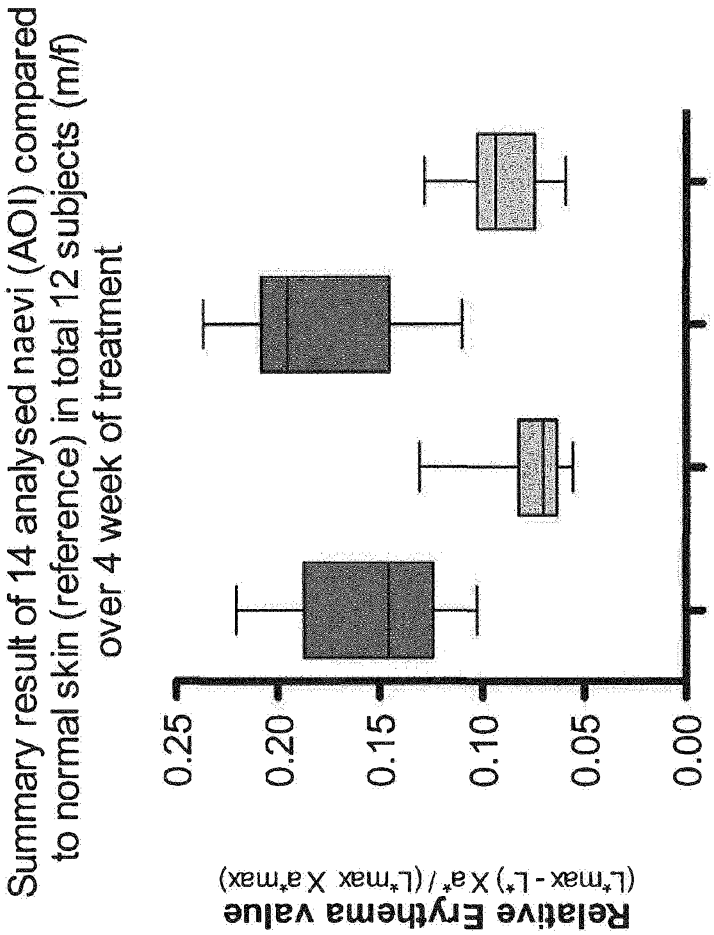
Summary result of 14 analysed naevi (AOI) compared to normal skin (reference) in total 12 subjects (m/f) over 4 week of treatment
Relative Erythema value
(L*max - L*) X a* / (L*max X a*max)
0.25
0.20
0.15
0.10
0.05
0.00
AOI (visit 1)
REF (visit 1)
AOI (visit 4)
Reference (visit 4)
analyzed skin regions

Figure 10 B