BMJ Open

Clinical trial on the efficacy and safety of NPC-15 for patients with xeroderma pigmentosum exaggerated sunburn reaction type: XP-1 study protocol for a multicentre, double-blinded, placebo-controlled, two-group crossover study followed by a long-term open study in Japan

Mariko Tsujimoto,[1] Yasumasa Kakei ,[2,3] Nozomi Yamano,[1] Takeshi Fujita,[4] Takehiro Ueda,[5] Ryusuke Ono,[1] Sae Murakami,[2] Shinichi Moriwaki,[6] Chikako Nishigori[1,7]

To cite: Tsujimoto M, Kakei Y, Yamano N, *et al*. Clinical trial on the efficacy and safety of NPC-15 for patients with xeroderma pigmentosum exaggerated sunburn reaction type: XP-1 study protocol for a multicentre, double-blinded, placebo-controlled, two-group crossover study followed by a long-term open study in Japan. *BMJ Open* 2023;**13**:e068112. doi:10.1136/bmjopen-2022-068112

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068112).

Received 07 September 2022
Accepted 13 March 2023

For numbered affiliations see end of article.

Correspondence to
Dr Yasumasa Kakei;
ykakei@med.kobe-u.ac.jp

ABSTRACT

Introduction Xeroderma pigmentosum (XP) is a rare intractable disease without a fundamental treatment, presenting with severe photosensitivity, freckle-like pigmented and depigmented maculae and numerous skin cancers before the age of 10 years without strict sun protection. About 70% of the patients exhibit extremely severe sunburn reactions and most of them develop neurological symptoms, including sensorineural hearing impairment and progressive peripheral and central nervous disorders beginning from childhood ages. In the preclinical study, we found that N-acetyl-5-methoxytryptamine was effective in suppressing skin tumour development in addition to improvement of auditory brainstem response in chronically ultraviolet-irradiated XP-A model mice.

Methods and analysis On the bases of the preclinical study, we conduct a clinical trial on the efficacy of NPC-15 for patients with XP with exaggerated sunburn reaction type by a multicentre, double-blinded placebo-controlled, two-group crossover study followed by a 52 weeks open study.

Ethics and dissemination Ethics approval is overseen by the Kobe University Institutional Review Board and Osaka Medical and Pharmaceutical University Institutional Review Board, and the study is conducted in accordance with the approved protocol. All participants will be required to provide written informed consent. Findings will be disseminated through scientific and professional conferences and peer-reviewed journal publications. The data sets generated during the study will be available from the corresponding author on reasonable request.

Trial registration number jRCTs051210181.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This clinical study is designed as a double-blinded crossover trial, followed by open study because the number of study patients is limited even in Japan.
⇒ The randomisation and evaluation of the minimum erythema dose, and the primary endpoint, along with the Efficacy and Safety Evaluation Committee are organised as independent of the investigators.
⇒ The limitations of this study include the duration of the open study, which is not enough for evaluating the new onset of skin cancer, and several genotypes are considered together.

INTRODUCTION

Xeroderma pigmentosum (XP) is an autosomal recessive genetic disorder associated with severe photosensitivity, freckle-like pigmented and depigmented maculae and skin cancers in sun-exposed areas. Numerous skin cancers can develop before the age of 10 years without strict sun protection. Furthermore, neurological symptoms, such as sensorineural hearing impairment and progressive peripheral and central nervous disorders beginning around 6 years of age, have also been observed in approximately 60% patients.[1 2]

The number of patients medically recorded to have XP in Japan is 300–600. However, estimated frequency of XP in the Japanese population, calculated by the number of patients diagnosed with the eight clinical subtypes

of XP (XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G and XP-V), is approximately 1:22 000 persons. To elaborate, the percentage of patients with XP-A accounts for about 50% of all XP in Japan, and 90% of them harbour the homozygous founder mutation of IVS3-1G>C (mutation from G (guanin) to C (cytosine) on intervening sequence (IVS) 3-1 side) in the *XPA* gene (responsible gene for XP-A); its carrier (heterozygote) ratio was 1:113 in the general population (heterozygous for the founder mutation in the *XPA* gene).[3] This discrepancy in the estimated number of patients (approximately 5600 patients) and those with officially recorded diagnoses was assumed to be because some patients were undiagnosed or were in facilities that limited their access to regular check-ups. Further, as the carrier data are based on archived pathological sections (from 1957 to 2011) stored at medical facilities in Hiroshima, it is possible that the frequency of carriers may have been higher in the previous era. Regardless, the frequency of XP is higher in Japan than in both Europe and the USA, whereby it is only observed at a rate of 1:1 000 000 people.[1 2]

XP is represented by eight clinical subtypes, seven of which (A-G) are caused by mutations in genes of the nucleotide excision repair (NER) pathway and one subtype (V) is NER proficient but deficient in translesion synthesis DNA polymerase η. Among Japanese patients with XP, XP-A accounts for 52.7% of the patients, followed by XP-V for 30.8%, XP-D for 7.3%, XP-F for 4.0%, XP-C for 2.7% and XP-G for 2.0% of patients.[2] Symptoms vary among groups. Patients with XP-A exhibit the lowest ability of DNA repair and the most severe cutaneous and neurological symptoms. The ratio of male to female patient incidence of XP is almost 1:1.

NER is the process of repairing DNA lesions caused by ultraviolet (UV) radiation, and NER defects, as in XP, result in the accumulation of DNA lesions that lead to carcinogenesis. While the pathogenesis of severe sunburn, pigmentary abnormalities and concomitant neurological symptoms is still unclear,[2] several hypotheses have been postulated; NER is involved in oxidative DNA lesions such as cyclopurine that accumulate in the neuronal cells of humans,[4 5] and patients with XP show an impaired mitophagy in their neuronal mitochondria due to oxidative stress.[6]

XP-A, XP-B, XP-D, XP-F and XP-G are categorised as exaggerated sunburn reaction types and patients with these subtypes manifest severe sunburn with minimum sun exposure and a prolonged reaction, with the erythema peak at 48–72 hours after UV exposure. In addition, these subtypes exhibit neurological symptoms to varying degrees. Patients with XP-A show severe photosensitivity from birth, freckle-like pigmented and depigmented maculae after UV exposure to the sun-exposed skin and development of skin cancer before the age of 10 years, if strict sun protection is not enforced. XP is associated with almost normal development in early childhood, with a usual observation of mild delays in speech and walking. However, neurological symptoms generally start with sensorineural hearing impairment at the age of 5–6 years, gait imbalance from 6 years and severe gait disturbance by 20 years. Breathing problems due to laryngeal dystonia, dysphagia and aspiration occur frequently and sensorineural hearing impairment and dysarthria cause severe communication challenges in the late teens. Patients with XP may develop skin cancer in childhood and adolescence, if not protected from the sun.[7–9]

Progressive central and peripheral neurological symptoms occur in almost all Japanese patients with XP-A, about 10% of patients with XP-D and some patients with XP-F and XP-G. The rate of neurological symptoms varies with age; however, they appear in almost all patients with XP-A in their mid-teens. There is no fundamental treatment for XP yet; although cutaneous conditions have improved over the last 30 years due to improved education for strict sun protection and early diagnosis and treatment for skin cancers with regular check-ups.[2] However, treatment or prevention of the progression of neurological symptoms is not possible. Symptomatic treatments by an interdisciplinary team, such as doctors from dermatology, paediatrics, neurology, otolaryngology, orthopaedics, ophthalmology, urology and dentistry, can assist with education for sun-protection, skin cancer checks, hearing aids and rehabilitation modalities to prevent secondary complications. Application of a UV-blocking film on windows in living spaces at home and schools is strongly recommended.

Anti-inflammatory drugs reduce UV-induced inflammation and skin tumour development in XP animal models[10]; XP animal models and/or patients' cells have shown that N-acetyl-5-methoxytyptamine suppresses inflammatory response and oxidative stress after UV irradiation. In addition, it suppresses skin tumour formation and improves auditory brainstem response (ABR) threshold, after chronic repetitive UV irradiation in XP-A model mice, suggesting that N-acetyl-5-methoxytyptamine can be a potential new treatment option for XP.

Although N-acetyl-5-methoxytryptamine was first identified as a hormone in the pineal gland by Lerner *et al*,[11] it is believed to have been derived from an antioxidant synthesised in photosynthetic cyanobacteria, 3 billion years ago, and have been conserved in almost all living species since then, with little change in its chemical structure.[12] N-acetyl-5-methoxytryptamine is responsible for regulating circadian rhythms and endogenous synthesis, and its secretion is regulated by the light/dark cycle, with the highest plasma concentrations at night. In addition to its pharmacological effects such as circadian rhythm regulation, there are many published references reporting N-acetyl-5-methoxytryptamine as a free radical scavenger and antioxidant.[13] It is particularly believed to act as an antioxidant within mitochondria.[12] Pharmacologically, N-acetyl-5-methoxytryptamine reduces the severity of injury in several disease models due to its effect on acute and chronic inflammation and central nervous system protection.

In Japan, Nobelpharma submitted a manufacturing and marketing authorisation application in April 2019, and a 0.2% granule of N-acetyl-5-methoxytryptamine was approved in March 2020 for the treatment of sleep difficulties associated with childhood neurodevelopmental disorders. However, as no drugs for XP have been approved and marketed in Japan and overseas, the development of an additional indication was promoted.

Furthermore, it has been shown that the level of N-acetyl-5-methoxytryptamine metabolites is reduced in patients with XP,[14] and there is a strong need to establish an early treatment for XP in actual clinical practice.

As this crossover study is to confirm the short-term efficacy of the drug to obtain a drug indication, the investigators have decided to target patients with XP with exaggerated sunburn reaction type.

In this trial, setting the primary endpoint will be difficult. An evaluation of the efficacy of the trial drug based on the progression level of neurological symptoms is desired. As the progression of neurological symptoms is gradual over the years, it is practically difficult to conduct a 10-year clinical trial on this disease. Furthermore, neurological symptoms differ with age, making the evaluation difficult. On the other hand, exaggerated and prolonged sunburn response is a lifelong symptom that is always and exclusively observed in patients with exaggerated sunburn type XP. Additionally, neurological symptoms are also observed in this type of XP. Furthermore, in our preclinical study, both cutaneous and neurological symptoms, such as ABR were ameliorated. Therefore, we theoretically considered that setting the primary endpoint as the improvement of minimum erythema dose (MED) is the best and most reliable (can be quantitatively evaluated) method for evaluation of drug efficacy in XP. However, irradiation of patients with XP with UV significantly increases the risk of skin cancers; therefore, patients with XP are educated to strictly avoid UV exposure. It has an ethical issue. After careful deliberation, we decided to set the primary endpoint as the MED at 72 hours to minimise UV exposure dose.

MATERIALS AND METHODS

Study design

This is a multicentre, placebo-controlled, double-blinded, randomised two-group crossover study followed by a long-term open study. The patient flowchart is shown in figure 1. As the number of patients with XP is limited and the half-life of NPC-15 is about 3 hours, a 2×2 crossover design was adopted. We ensured that the carry over effect would not affect the research results by setting the washout period to 14 days.

Study setting

This study will be performed at Kobe University Hospital and Osaka Medical and Pharmaceutical University Hospital. All study data will be stored and archived in the data centre of DOT World using Viedoc (Viedoc Technologies AB, Uppsala, Sweden), an electronic data capture (EDC) system for clinical research, to manage the data and protect confidentiality before, during and after the trial.

Purpose

The purpose of this study is to evaluate the efficacy and safety of orally administered NPC-15 (Nobelpharma, Tokyo, Japan) before bedtime at a dose of 0.5–4 mg (0.067 mg/kg) per day for 62 weeks (crossover study, 10 weeks; open study, 52 weeks) in patients with exaggerated sunburn reaction type XP.

Endpoints

Primary endpoint

The primary endpoint is the MED, 72 hours (±6 hours) after UV irradiation on the 15th day (crossover period I and crossover period II) of investigational drug administration. A UV-irradiated examination is a burdensome examination for patients with XP; therefore, determination of the study's primary endpoint was done after sufficient discussion, as mentioned in the Introduction section. The 'MED' is defined as the minimum dose that elicits very faint, but discernible erythema (NOT USUAL SUNBURN). Usually, MED is measured 24 hours after UV irradiation. However, delay of the erythematous peak is a characteristic of exaggerated sunburn type XP. In this clinical trial, MED at 72 hours will be evaluated; therefore, the irradiation dose can be minimised. The upper limit of the irradiation dose will be set between 30 and 60 mJ/cm^2, considering the degree of photosensitivity based on the patient's age (skin thickness) and genetic diagnosis. The irradiated area will be set in a way such that it does not overlap for both the left and right back, during crossover period I and II, respectively.

Secondary endpoint

The secondary efficacy endpoints will be the following:

1. MED at 24 hours, 48 hours and 96 hours (±6 hours) after UV irradiation on the 15th day (period I and period II) of investigational drug administration.
2. Evaluation of Melanin Index regarding the pigmented area in MED judgement area.
3. Pigmented maculae inspection (number, area and colour tone).[15]
4. Neurological symptoms (neurological severity scale score on XP,[16] hearing test and 5 m gait test).
5. Presence or absence of onset of acute skin symptoms.
6. Presence or absence of skin cancer.

The secondary endpoint for safety is the presence or absence of any adverse events and the intensity of drowsiness and dizziness (Visual Analogue Scale score) associated with the conduct of this clinical study.

Eligibility criteria

Inclusion criteria

Patients who meet the following criteria will be included in the study:

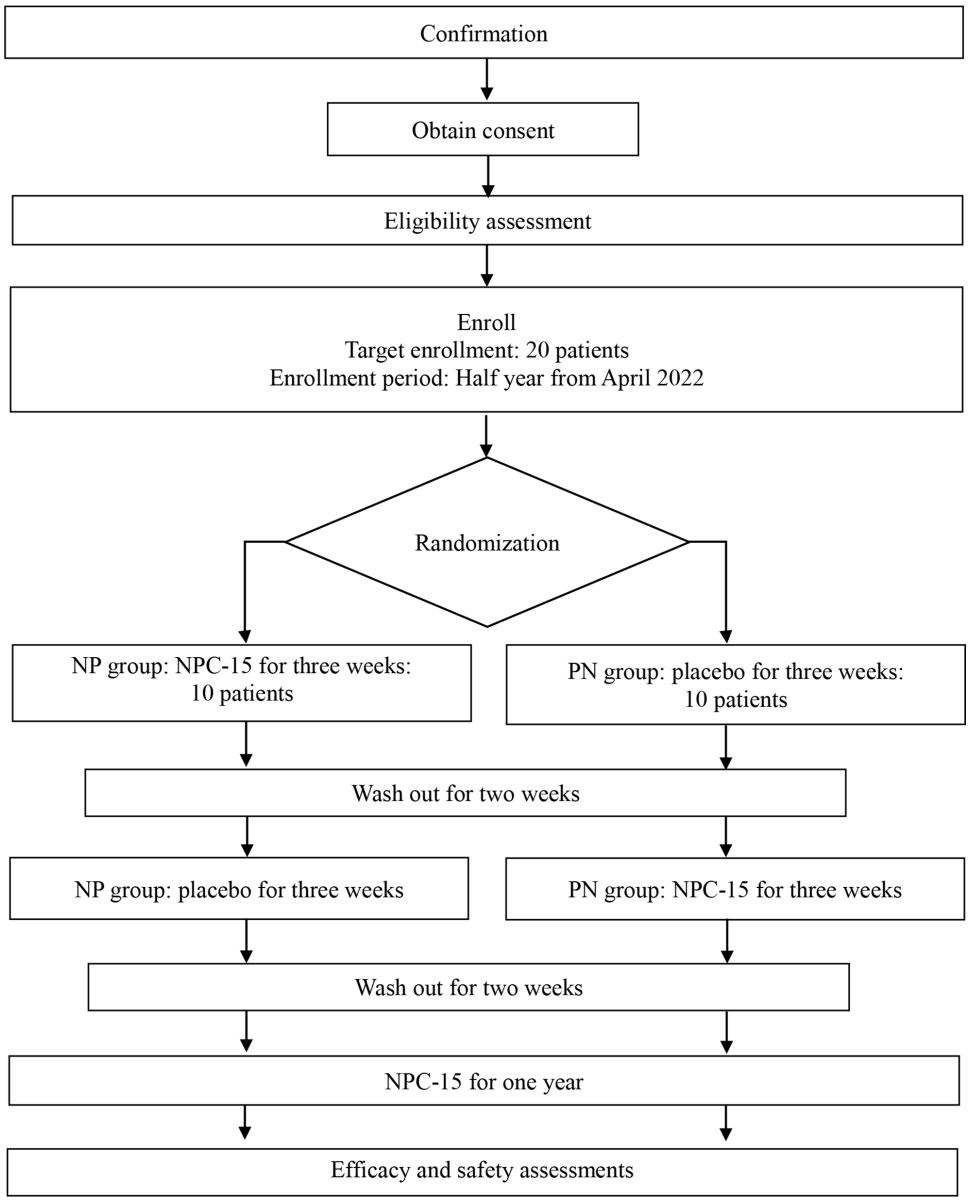

Figure 1 Flow chart of participants. NP, NPC-15 to placebo; PN, placebo to NPC-15.

1. Patients with XP (according to the XP diagnostic criteria by the Japan Dermatology Society, 2015) who have been diagnosed with exaggerated sunburn reaction type (XP-A, XP-B, XP-D, XP-F and XP-G) by genetic testing.
2. Patients aged 1 year or older with a weight of 7.5 kg or more at the time of consent. However, patients under 6 years of age will be enrolled after confirming the safety for the first 10 cases of the patients aged 6 years or older during the crossover study by the Safety Evaluation Committee.
3. Patients (or their caregivers/guardians) who have provided written informed consent to participate in this study.

Exclusion criteria

Patients with the following criteria will be excluded from the study:

1. Patients with a history of allergies to N-acetyl 5-methoxytryptamine or ramelteon.
2. Patients receiving other investigational drugs (including placebo) within the 4 months prior to obtaining consent.
3. Patients who have been using N-acetyl-5methoxytryptamine (including health foods containing melatonin as the principal component) and fluvoxamine maleate (Luvox, Depmerol, etc) in the 4 weeks prior to the start of drug administration.
4. Pregnant, lactating women, women who wish to become pregnant during the study period or women who are fertile and cannot accept an effective contraceptive method.
5. Patients deemed inappropriate by the investigators for participation in this clinical study.

Randomisation

All patients who provide consent to participate and fulfil the sampling criteria will be randomised. Patients will be randomly assigned to either the NPC-15-placebo (NP) or placebo-NPC-15 (PN) group with a 1:1 allocation using the permutation random block method stratified by category (whether XP genotype is XP-A or not). The block size will not be disclosed to ensure that blinding is maintained. The allocation sequence for the randomisation method will be generated by a person in charge from DOT world company, contract research organisation. The trial participants, care providers and endpoint assessors will be blinded. Either the principal or subinvestigator will send a patient enrolment form by EDC to the data centre. The staff at the data centre will confirm the patient's eligibility and issue the patient enrolment confirmation form containing the eligibility judgement, the randomisation assignment result from the generated random sequence and the enrolment number. The form will then be sent to the principal investigator or subinvestigator.

Data collection and management

Either the principal investigator or subinvestigator will enter the case report form (CRF) data for each patient into the EDC system. The principal investigator will confirm the completion and correctness of entered CRF data, electronically sign the CRF in Viedoc and make a printout of the signed CRF for maintaining records. The CRF printout will be retained for audit trail purposes. In case of queries about the CRF data, the principal investigator or subinvestigator will promptly respond. Only the biostatistician will have access to the final data set.

Monitoring and audit

The study will be monitored to ensure protection of the human rights and welfare of the patients, safe progression of study in accordance with the protocol, and proper collection of applicable regulatory requirements under Good Clinical Practice and data. The principal investigator will appoint someone to responsibly monitor the study. The items to be checked at monitoring are specified in the written procedure for the implementation of study monitoring. For quality assurance, the study will be examined four times, that is, before initiation of the clinical trial, after the first patient in, before the last patient in and before completion of the integrated study report, to determine that it is being conducted in accordance with the protocol and written procedures, independently and separately from the routine activities of monitoring.

Intervention and treatment protocol

The NPC-15 0.2% granules sold by Melatobel for paediatrics are manufactured at Nobelpharma. The placebo formulation is the same except that it does not contain N-acetyl 5-methoxytryptamine.

NP group will receive NPC-15 for the first 3 weeks, followed by the placebo for 3 weeks after a 2-week drug holiday. PN group will receive the placebo for the first 3 weeks, followed by NPC-15 for 3 weeks after a 2-week drug holiday. The investigational drug will be administrated orally one time per day at a dose of 0.5–4 mg (0.067 mg/kg) before bedtime.

The relationships between the interventions, endpoints, other assessments and visits for the patients in this study are shown in online supplemental tables 1 and 2.

Statistical analysis

Analysis set

A summary of the planned statistical analysis for this study is provided below. The final analysis will be performed after data from the patients have been obtained and fixed at the end of the follow-up period.

The full analysis set is the set of randomised patients who receive at least one dose of the study drug. The per-protocol set is the subset of patients in the full analysis set who sufficiently comply with all aspects of the clinical trial protocol, including the drug administration methods and schedule. The safety analysis set is the set of patients who receive at least one dose of the study drug. In this study, the safety analysis set is the same as the full analysis set.

Statistical analysis

Statistical analyses will be conducted using the SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA). The patient baseline characteristics will be summarised using arms and periods. For continuous variables, the summary statistics (number of patients, mean, SD, minimum, median and maximum) will be calculated. For nominal variables, the categorical frequency and proportion will be presented. Missing scores for MED difference will be replaced by zero, and no imputation will be performed for any further endpoints.

For the crossover study, we will conduct the analysis under the assumption that there is no carryover effect due to a short half-life; therefore, a 2-week washout period will take place after period I. The analysis will be based on the difference in endpoints between period I and II for each patient. The difference between the mean endpoints (MED in each time point, Melanin Index and concentrations of oxidative stress markers) of the NPC-15 and placebo and its 95% CI will be estimated. Statistical significance will be assessed using the Student's t-test, with a significance level for hypothesis testing of 2.5% (one-sided).

For the open study, neurological symptoms at 52 weeks after the open study will be compared with those before the study using McNemar's, one-sample t-test, or Wilcoxon rank-sum test according to the type of each endpoint. The difference in oxidative stress marker (malondialdehyde, 8-hydroxy-2-deoxyguanosine, hexanoyl-Lys) concentrations before and after the open study will be assessed using a one-sample t-test.

The change of facial pigmented maculae at the start and end of the study, which will be examined according to number, area and colour tone, will be analysed using the Wilcoxon rank-sum, one-sample t-test and McNemar's

test, respectively. McNemar's test will be used to compare the incidence of acute cutaneous symptoms and development of skin cancer during the 62 weeks study period and 62 weeks before the study.

The number of adverse events and their frequency and percentage of occurrence will be summarised according to time, overall currency and by treatment.

For evaluation of delayed sexual maturation or development, no statistical test will be performed and secondary sexual characteristics and blood hormone (prolactin) levels in each patient will be individually described.

Sample size calculation

The primary outcome will be to compare the changes of MED in crossover period I and II between the two groups. MED of patients with XP is approximately 5–10 times smaller than that of healthy controls. For healthy controls, a difference of 10 mJ/cm^2 in MED is apparently sufficient in the clinical setting. Therefore, we thought the difference of 1–2 mJ/cm^2 should be clinically sufficient for patients with XP. If we compare irradiation areas on one side of a child's back, avoiding apparently curved areas, we postulate that 10 areas are the limit. Trying to evaluate all participants with the same irradiation dose difference and considering that 10 areas are limit for children, a 3 mJ/cm^2 difference per area was considered most appropriate. The minimum effect of improved MED should be larger than this irradiation dose difference. It is reasonable to assume that the difference in MED between the placebo and actual drug is not as great as the difference in MED between healthy participants and patients with XP; in fact, it is possibly much lower. From the above observation, we estimated the difference in change of MED between the placebo and actual drug to be approximately 4.4 mJ/cm^2, which was 1/5th of the difference between the mean MED at 24 hours after irradiation in seven healthy participants (54.3 mJ/cm^2) and 28 patients with XP (31.9 mJ/cm^2). We believe that a difference of 4.4 mJ/cm^2 is sufficient to reduce the biological effects of UV exposure for patients with XP with photosensitivity. The SD was assumed to be 6.0 mJ/cm^2, two times per day the irradiation unit dose for MED examination. Differences in NPC-15 and placebo in a crossover design can be substituted for differences in period between groups. The difference in period in NP group is denoted by (period I (NPC-15) – period II (placebo)) and the difference in period in PN group by (period I (placebo) – period II (NPC-15)). Thus, the difference between the two groups can be written as ((period I (NPC-15) – period II (placebo)) – (period I (placebo)) – period II (NPC-15)) = 2 × ((NPC-15) – (placebo)). We expected a difference of 4.4 mJ/cm^2 and an SD of 6.0 mJ/cm^2 between the two groups in MED. Using a one-sided t-test with a significance level of 0.025, we need eight patients in each group to have at least 80% power. Assuming a few dropouts, a total of 10 patients in each group are required.

Study period

This study is based on the current version of the study protocol (V.1.2, last updated on 1 June 2022). The study was first approved on 24 January 2022 by the Institutional Review Board of Kobe University, Graduate School of Medicine and authorised by the Pharmaceutical and Medical Devices Agency. Participant recruitment began on 1 April 2022. The expected date of completion (last visit of the last patient) is 15 December 2023.

Patient and public involvement

Patients and the public were not involved in the development of the research questions, selection of endpoint measures, study design, patient recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical review committee. As mentioned in the individual consent form, participants may obtain access to the final results of the study through the principal investigator.

Ethics and dissemination

The study is being conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and all applicable regulatory requirements. Ethics approval is overseen by the Kobe University Institutional Review Board (210040) and Osaka Medical and Pharmaceutical University Institutional Review Board, and the study is conducted in accordance with the approved protocol.

As described in the Introduction section, measurement of MED involves unavoidable ethical issues. We explained this point, along with the following points to the participants (or their caregivers/guardians): (1) difficulties other than the MED measurement in assessing the efficacy of XP therapeutics over a certain period of time; (2) that the dose of UV irradiation in this clinical trial was set lower than that of the UV examination conducted at the time of diagnosis; and (3) that we considered the possibility of developing cancer with MED measurements in this trial to be sufficiently low. Before genetic diagnosis became mainstream, at least 50 patients with XP with exaggerated sunburn reaction type underwent more than 60 mJ/cm^2 UV irradiation on their back for diagnostic purposes in our hospital; however, none of them developed skin cancer on the tested sites, where patients are rarely exposed to the sun.

Written informed consent is obtained from all participants before any study procedure is performed. The participants (or their caregivers/guardians) will have the opportunity to review the participant consent form and provide acknowledgement of complete understanding of the study procedures. Informed consent will be administered by a suitably qualified and experienced individual delegated to this task by the principal investigator. For participants under 18 years of age, or individuals over 20 years of age who are unable to provide consent due to intellectual disability, consent is obtained from

the substitute/caregivers/guardians. The protocol was submitted to the Japan Registry of Clinical Trial.

Author affiliations
[1]Dermatology, Kobe University Graduate School of Medicine School of Medicine, Kobe, Japan
[2]Clinical & Translational Research Center, Kobe University Hospital, Kobe, Japan
[3]Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine School of Medicine, Kobe, Japan
[4]Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine School of Medicine, Kobe, Japan
[5]Neurology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
[6]Dermatology, Osaka Medical and Pharmaceutical University, Takatsuki, Japan
[7]Hyogo Red Cross Blood Center, Kobe, Japan

Acknowledgements We would like to thank Editage (http://www.editage.jp) for English language editing.

Contributors MT obtained the grant funding and drafted the manuscript. RO, TF and TU obtained the grant funding and reviewed the manuscript. YK managed the study and drafted the manuscript. CN is the chief investigator who conceived and designed the study and obtained the grant funding and drafted the manuscript. SMu designed the statistical analysis plan and reviewed the manuscript. NY and SMo reviewed the manuscript. All authors provided final approval of the manuscript.

Funding This work is supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP15ek0109028h0002 (CN, MT and RO), 21ek0109450h0002 (CN, MT, RO and TF), 21ek0109562h0001 (CN, MT, RO, TF and TU) and by Ministry of Health, Labor and Welfare under Grant number 20FC1043 (CN and TU). The grant funder for this study played no role in the study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. The funding agency can be contacted at the following email address: rare-koubo@amed.go.jp.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Yasumasa Kakei http://orcid.org/0000-0002-5997-514X

REFERENCES

1 Moriwaki S, Kanda F, Hayashi M, *et al*. Xeroderma pigmentosum clinical practice guidelines. *J Dermatol* 2017;44:1087–96.
2 Nishigori C, Nakano E, Masaki T, *et al*. Characteristics of xeroderma pigmentosum in Japan: lessons from two clinical surveys and measures for patient care. *Photochem Photobiol* 2019;95:140–53.
3 Hirai Y, Noda A, Kodama Y, *et al*. Increased risk of skin cancer in Japanese heterozygotes of xeroderma pigmentosum group A. *J Hum Genet* 2018;63:1181–4.
4 Kuraoka I, Bender C, Romieu A, *et al*. Removal of oxygen free-radical-induced 5',8-purine cyclodeoxynucleosides from DNA by the nucleotide excision-repair pathway in human cells. *Proc Natl Acad Sci U S A* 2000;97:3832–7.
5 Wang J, Cao H, You C, *et al*. Endogenous formation and repair of oxidatively induced G [8-5 M] T intrastrand cross-link lesion. *Nucleic Acids Res* 2012;40:7368–74.
6 Fang EF, Scheibye-Knudsen M, Brace LE, *et al*. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD (+) /SIRT1 reduction. *Cell* 2014;157:882–96.
7 Nishigori C, Moriwaki S, Takebe H, *et al*. Gene alterations and clinical characteristics of xeroderma pigmentosum group A patients in Japan. *Arch Dermatol* 1994;130:191–7.
8 Satoh Y, Nishigori C. Xeroderma pigmentosum: clinical aspects. *Gann Monograph on Cancer Research* 1988;35:113–26.
9 Masaki T, Tsujimoto M, Kitazawa R, *et al*. Autopsy findings and clinical features of a mild-type xeroderma pigmentosum complementation group A siblings: 40 years of follow-up. *JAAD Case Rep* 2019;5:205–8.
10 Kunisada M, Hosaka C, Takemori C, *et al*. CXCL1 inhibition regulates UVB-induced skin inflammation and tumorigenesis in xpa-deficient mice. *J Invest Dermatol* 2017;137:1975–83.
11 Lerner AB, Case JD, Mori W, *et al*. Melatonin in pineal nerve. *Nature* 1959;183:1821.
12 Reiter RJ, Rosales-Corral S, Tan DX, *et al*. Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. *Cell Mol Life Sci* 2017;74:3863–81.
13 Hardeland R. Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance. *Endocrine* 2005;27:119–30.
14 Okoshi Y, Tanuma N, Miyata R, *et al*. Melatonin alterations and brain acetylcholine lesions in sleep disorders in Cockayne syndrome. *Brain Dev* 2014;36:907–13.
15 Bossart S, Ramelet A-A, Willenberg T, *et al*. Skin hyperpigmentation index facilitating quantification of hyperpigmentation in clinical practice. *Dermatology* 2021;237:486–8.
16 Nakano E, Masaki T, Kanda F, *et al*. The present status of xeroderma pigmentosum in Japan and a tentative severity classification scale. *Exp Dermatol* 2016;25 Suppl 3:28–33.

Table 1. Summary of study assessments and procedures in the crossover period

	Study period														
	Screening period		Crossover period I							Crossover period II					
			Treatment period NPC-15 or Placebo						Washout	Treatment period Placebo or NPC-15					Washout
	Enrollment	Allocation	Day1[1]	Day 15[1]	Day 16[1]	Day 17[1]	Day 18[1]	Day 19[1]	Day 22–35[2]	Day 1[1]	Day 15[1]	Day 16[1]	Day 17[1]	Day 18[1]	Day 19[1]	Day 22–35[2]
Informed Consent[3]	X															
Baseline data	X															
Enrollment	X															
Prescription			←	—	—	—	—	→			←	—	—	—	→	
UV irradiation[4]				X							X					
MED[4]					X	X	X	X				X	X	X	X	
Melanin index										X						

neurological severity scale score[5]	X															
hearing test[6]	X															
5-meter walk test[7]		X														
Acute skin symptom	X [8]															
Skin cancer	X [8]															
urine test for oxidative stress marker[9]		X						X							X	
Laboratory test	X							X							X	
Secondary sexual characteristics status[10]	X															
Adverse events			←												→	

drowsiness and dizziness		X			X							X				
Body weight		X														
Medication status				X	X	X	X	X		X	X	X	X	X	X	
Concomitantly administered medications[11]		←														→

[1] In the case of five or more consecutive holidays, including weekends and national holidays such as New Year's Eve and Golden Week, the allowable range for the treatment period is ± 3 days, and the allowable range for the washout period after the crossover study period I and II is +22/-4, and ± 4 days, respectively.

[2] Allowance (-3~＋21) is based on the point of day 35.

[3] Consent should be obtained within 12 weeks prior to drug allocation.

[4] Visit tolerance on the UV test day is ± 2; however, evaluation should be made at 24, 48, 72, and 96 hours ± 6 hours after the test day. Re-evaluation is prohibited.

[5] Neurologic severity scale scores will be evaluated in patients aged 3 years or older.

[6] Methods of hearing test (pure-tone audiometry or conditioned play audiometry) will be recorded in the medical records.

[7] The 5-meter walk test will be conducted including the patients who wear braces when the principal/participating investigator deems the patient can tolerate the test. The presence or absence of brace or the type of brace used will be recorded in the medical records. When the patient wears the brace, the tests at visit 1 and Visit 305 will be conducted using the same brace as far as possible, and if the brace is changed, the kinds of brace and the reason for the change of brace will be described in the medical records.

[8] Data will be collected within 62 weeks prior to administration of the study drug.

[9] Laboratory urine test: oxidative stress markers (Malondialdehyde, 8-hydroxy-2-deoxyguanosine, Hexanoyl-Lys) and N-acetyl 5-methoxytryptamine metabolites (6-sulfatoxymelatonin).

[10] Confirmation of secondary sexual characteristics status and measurement of prolactin levels in blood. To be performed on patients between 10 and 17 years of age.

[11] Four weeks prior to the initiation of the study drug.

Table 2. Summary of study assessments and procedures in the open period

	Open trial				
	Day1	Week 13	Week 26	Week39	Week52
Prescription (NPC-15)	←				→
Melanin index	X				
Facial pigmentation	X				X
Neurologic severity scale score [b]					X
Hearing test [c]					X
5-meter walk test [d]					X
Acute skin symptoms					X
Skin cancer					X
Laboratory test for Research (urine)[e]	X		X		X
Laboratory tests (blood and urine) [f]					X
Secondary sexual					X

characteristics status [g]					
Adverse events	←	—	—	—	→
drowsiness and dizziness	X	X	X	X	X
Body weight	X	X	X	X	
Medication status		X	X	X	X

[a] The study will be conducted only on patients who are deemed by the principal/sub-investigator at Visit 305 (after 52 weeks of the open study), to require a visit to the hospital for evaluation of adverse events, etc.

[b] Neurologic severity scale score will be evaluated in patients aged 3 years or above.

[c] Methods used for testing hearing (pure-tone audiometry or conditioned play audiometry, etc.) will be recorded in the medical records.

[d] The 5-meter walk test will be conducted including the patients who wear the brace when the principal/participating investigator deems the patient can tolerate the test. The presence or absence of brace or the type of brace used will be recorded in the medical records. When the patient wears the brace, the tests at visit 1 and Visit 305 will be conducted using the same brace as far as possible, and if the brace is changed, the kinds of brace and the reason for the change of brace will be described in the medical records.

[e] Urine examination for research use: Oxidative stress markers (Malondialdehyde,

8-hydroxy-2-deoxyguanosine, Hexanoyl-Lys) and N-acetyl 5-methoxytryptamine metabolites (6-sulfatoxymelatonin).

[f] Urine examination: Urinary protein and urinary urobilinogen.

[g] Confirmation of secondary sexual characteristics status and measurement of prolactin levels in blood. To be performed on patients between 10 and 17 years of age.