

Study protocol: Sonidegib for Nevoid Basal Cell Carcinoma (Gorlin) Syndrome and EADO stage IIb Sporadic BCC, a phase II Study (SIBLINGS TRIAL).EU CT n. 2024-515989-14-00

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Abstract

Background:

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), or Gorlin syndrome, is a rare genetic condition characterized by multiple basal cell carcinomas (BCCs) and increased risk of other malignancies. In this population, surgery and radiotherapy are often unfeasible, making systemic treatment a necessity. Similarly, some sporadic BCC patients present extensive lesions, classified as difficult-to-treat (EADO stage IIb). Hedgehog-inhibitors (HHIs), such as vismodegib and sonidegib, have demonstrated efficacy in advanced BCCs, including NBCCS. While both agents act on the same pathway, sonidegib has shown favorable pharmacokinetics and potentially longer progression-free survival. However, class-specific adverse events (AEs) often lead to treatment discontinuation, limiting long-term benefits. Pulsed treatment schedules may mitigate toxicity and improve compliance.

Methods:

This is a phase II, single-arm, open-label study evaluating a tailored sonidegib schedule in adults with NBCCS or sporadic EADO stage IIb BCC patients. Eligible participants are aged 18–50, ECOG PS 0–1, HHI-naïve, not candidates for surgery or radiotherapy. Following a 16-week induction phase with daily sonidegib (200 mg), responders enter a 24-week maintenance phase using a pulsed 2:2 schedule (2 weeks on, 2 weeks off). Temporary suspensions (≤ 3 weeks) and dose reductions are permitted for grade ≥ 3 AEs. Response is assessed via RECIST at clinical visits, focusing on objective response rate (ORR), duration of response (DOR), and emergence of new lesions. The primary endpoint is treatment compliance, defined by the discontinuation rate. Secondary outcomes include safety, quality of life, and BCC control. A sample size of 15 patients provides 80% power to detect a reduction in discontinuation from 54% (from literature) to 20%.

Discussion:

Sonidegib shows efficacy in NBCCS and unresectable sporadic BCC but its toxicity profile often limits treatment duration. This study explores whether a planned pulsed dosing strategy can improve tolerability, reducing discontinuation while maintaining clinical benefit. Early evidence suggests this approach may extend treatment duration, improve quality of life, reduce relapse rates and emergence of new lesions. Limitations include small sample size and slow recruitment, inherent to the rarity of NBCCS and stringent eligibility criteria. Nevertheless, the study could provide valuable insights for optimizing long-term management in these high-need populations.

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Background

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Gorlin syndrome, is a rare inheritable condition characterized by the development of numerous basal cell carcinomas (BCC)¹, often emerging

early in life and recurring throughout the patient's lifetime, as well as an elevated risk of developing medulloblastomas and rhabdomyosarcomas². While surgery represents the mainstay for BCC treatment, in NBCCS patients it may represent a clinical challenge, owing to number, size and the consequent functional and aesthetic results; some non-NBCCS patients with multiple BCCs lesions may also present similar clinical challenges, particularly those classified as EADO-stage IIb³.

Collectively, these patients represent a uniquely difficult-to-treat population due to frequent necessity of surgical removal of early-stage lesions and contraindication to radiation therapy.

Knowledge regarding the pathogenetic role of the hedgehog (Hh) signaling pathway, a key driver in BCC development primarily through inactivating mutations in *PTCH1* and *SMO*⁴, has led to development of oral hedgehog inhibitors (HHIs), such as vismodegib and sonidegib⁵. Both agents have proven to be highly effective in locally advanced (LA) sporadic BCCs as well as in reducing the development of new BCC lesions in NBCCS^{6,7,8}.

These agents share a similar mechanism of action, while differing in their pharmacokinetics properties: sonidegib is characterized by a higher distribution volume and increased lipophilicity, leading to higher skin concentrations relative to plasma^{9,10}.

Although a head-to-head comparison of these agents in the setting of advanced BCC is not available, indirect comparison suggest that sonidegib may offer slightly higher objective response rate (ORR), 74.2% vs 60.3%, based on RECIST-like criteria, and a longer duration of response (DOR), with similar complete response (CR) rates (28.8% for sonidegib vs 31.7% for vismodegib)^{7,8}. Furthermore, a difference in progression-free survival (PFS) is appreciated: with sonidegib recording intervals of up to 2 years compared to less than 12 months for vismodegib^{7,8}. Despite their efficacy, both agents are associated with class-specific adverse events (AEs), such as muscle spasms (54–71% for sonidegib - vismodegib), dysgeusia (44–58%), hair loss (49–66%), fatigue (32–39%), and weight loss (44–56%); frequently leading to treatment discontinuation¹¹. Sonidegib appears to have significantly lower AEs' incidence and slower time to AEs onset, determining an increase in treatment duration. In this context schedule modulation may offer a possibility to extent treatment duration and drug exposure¹²; trials such as BOLT and ERIVANCE permitted protocol-defined treatment breaks, with up to 3–4 weeks of interruptions, resulting in overall treatment exposure of 11 and 12.9 months respectively^{13,14}.

As therapy breaks to control AEs are more frequent in clinical practice, impacting positively on overall treatment compliance and effectiveness, development of intermittent, personalized HHI regimens, may improve compliance, extent of treatment duration, enhance quality of life, maintaining long duration of responses^{15,16}. In SONIBEC trial, a pulsed sonidegib maintenance schedule post-complete response (CR) led to reduced relapse rates and fewer AEs¹⁷. For NBCCS patients, who require long-term therapy to prevent lesion recurrence, personalizing treatment schedules could prove especially valuable.

Given these considerations, the issue of schedule personalization to provide longer HHI exposure acquires critical importance in NBCCS patients, a population in which prolonged chronic exposure is required to prevent new BCC development. Daily administration of vismodegib in this context resulted in a drug discontinuation rate of 54% due to AEs, with lower rates (23%) recorded when intermittent dosing regimens were employed in subjects affected by multiple BCC, including NBCCS patients¹⁵.

Methods/Design

This is a single arm, open-label, multicentric, phase II clinical trial evaluating the feasibility, compliance, efficacy and safety of a personalized, pulsed sonidegib schedule in adult patients with NBCCS and sporadic EADO stage IIb BCC.

We aim to enroll adult patients, aged 18 to 50 years, with a histologically confirmed diagnosis of NBCCS or sporadic BCC, classified as difficult to treat and not amenable for surgery or radiotherapy after a multidisciplinary evaluation and followed in Italian reference hospitals. Additional inclusion criteria are ECOG PS 0 or 1, no prior systemic therapy with HHIs, no evidence of distant metastatic disease (M1), visceral and/or distant nodal. Exclusion criteria include: any malignancy within 5 years prior to enrollment (other than previous BCC or squamous cell carcinoma of the skin that has undergone potentially curative therapy, curatively resected in situ cervical and/or breast cancers or low-grade prostate cancers).

All enrolled patients will receive oral sonidegib 200mg daily for 16 weeks (4 cycles) as an induction phase. In case of an objective response, this will be followed by a maintenance phase with an intermittent dosing schedule: 200mg daily for 2 weeks followed by a 2-week drug holiday (2:2 schedule), for a total of 24 weeks. Dose reductions and treatment interruptions (up to three weeks) to manage grade 3 and 4 AEs might be employed as per clinical practice during both the induction and maintenance phases (Fig. 1).

After 24 weeks of maintenance, subjects will enter the safety follow-up phase of the trial. If no progression is detected and no permanent treatment discontinuation has occurred, the choice to continue sonidegib treatment will be left to a shared decision between the patient and the physician.

Primary objective will be to evaluate treatment compliance of the tailored pulsed sonidegib schedule through the assessment of treatment discontinuation rate, due to AEs at 40 weeks from study entry. Planned secondary endpoints will be activity, efficacy, safety and quality of life will be assessed as secondary objectives through ORR, DOR, CTCAE v5.0 and EORTC QLQ C30 score.

Tumor response will be assessed using RECIST criteria, focusing on up to five target lesions identified by site investigators. Complete (CR) and partial responses (PR), disease progression (PD) will be recorded. Response to treatment will be measured starting from the beginning of sonidegib continuous dosing and will be evaluated throughout the study at each clinical visit. Special interest is reserved to the evaluation at the beginning of the intermittent dosing regimen to identify patients achieving CR.

Up to five target lesions, deemed most representative by the center's investigators, will be considered for evaluation.

Duration of response (DOR) will be measured from the first achievement of PR to the development of PD in a target lesion or the appearance of a new BCC. New cutaneous BCC will be considered as PD if the lesion is > 5 mm and can be clearly documented as not being previously present. Examination of the lesion area and all relevant anatomical areas will be done at scheduled assessment visits, pictures will be taken at each visit for the measurable disease.

Previous experience of HHIs in NBCCS population recorded a discontinuation rate due to AEs of 54%. Our hypothesis is that a pulsed dosing of sonidegib in NBCCS subjects after induction phase with daily sonidegib can lead to an increased treatment compliance. A sample size of 15 subjects is calculated to detect a reduction in treatment discontinuation from 54% to 20% with an 80% power and an alpha and beta error of 0.05 and 0.2, respectively.

Descriptive statistics will be used to summarize baseline characteristics and the secondary objectives.

Discussion

This trial addresses a key limitation in the long-term management of NBCCS and difficult-to-treat sporadic BCCs: treatment discontinuation due to hedgehog inhibitor (HHi)-related toxicity. Despite their proven efficacy, continuous daily administration of HHIs like vismodegib and sonidegib is often unsustainable over time. High rates of adverse events (AEs) lead to poor adherence and premature treatment discontinuation, influencing both clinical benefit and quality of life¹¹. Moreover, the use of vismodegib demonstrated to reduce the emergence of new lesions in a randomized trial, thus highlighting the possible preventative role of this class of drugs in genetic syndrome¹⁸. This continuous administration of the drug however it is not without toxicities; in the Tang trial, 27% of patients had stopped the drug due to adverse events.

Pulsed sonidegib regimens represent a more tolerable and sustainable therapeutic approach, balancing efficacy, patient adherence and well-being^{13,14}. Our hypothesis is that an intermittent schedule following an initial induction phase may prolong treatment exposure, reduce toxicity, and thereby improve overall compliance, particularly in chronic conditions such as NBCCS. This concept aligns with emerging evidence and real-world practice, where personalized schedules and treatment holidays have been associated with extended therapeutic durations and better tolerability, without compromising efficacy¹⁹.

From a practical and operational standpoint, the main challenge is represented by the slow recruitment, affected by the rarity of NBCCS and the stringent eligibility criteria, such as the upper age limit (50 years) and the exclusion of patients with prior systemic therapies may further restrict the pool of potential participants. Additionally, the single-arm, open-label design may reduce the ability to draw definitive causal inferences and to perform comparative analyses.

Moreover, maintaining consistent follow-up, adherence monitoring, and standardized lesion documentation (via photographs and clinical evaluations) represents a logistical burden, particularly in a multicenter setting.

Given the long-term nature of therapy in NBCCS and the difficult balance between disease control and treatment tolerability, individualized and tailored care plans, with a focus on patient preferences and quality of life, are essential. While this study is not powered to demonstrate superiority in progression-free survival or overall survival, it could provide valuable evidence on the potential benefits of pulsed HHI therapy, giving solid scientific bases for treatment personalization. Positive results would support the development of more flexible schedules and could serve as the basis for larger, comparative trials.

In conclusion, this trial addresses an important unmet need in the management of NBCCS and LA sporadic BCCs by evaluating an innovative, patient-centered approach to HHI therapy. Despite inherent limitations, findings could allow to improve real-world care for this patient population, improving tolerability and long-term adherence through a rationalized and personalized treatment schedule.

Abbreviations

NBCCS

Nevoid Basal Cell Carcinoma Syndrome

BCC

Basal cell carcinoma

LA

locally advanced

ORR

objective response rate

CR

complete response

PR

partial response

PD

disease progression

PFS

progression-free survival

DOR

duration of response

AEs

adverse events

HHIs

Hedgehog inhibitors

QoL

quality of life

ECOG PS

Eastern Cooperative Oncology Group Performance Status

Declarations

Ethics approval and consent to participate

The responsible investigator will ensure that this study is conducted in agreement with the study protocol, either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to good clinical practice guidelines (GCP-ICH).

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Centre. This must be done in accordance with the national and local regulatory requirements. For European Union member states, the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative.

The protocol and its annexes have been reviewed and approved by the competent Independent Ethics Committee(s) ("IEC"), Comitato Etico Territoriale Lombardia 5, and by the Italian Pharmacovigilance Agency (AIFA).

CTIS ID 29828.

Consent for Publication:

Not applicable. This protocol does not contain any individual person's data in any form.

Availability of data and materials

Not applicable.

Competing interests

PB: Sun Pharma Italia Srl

CR: Honoraria from Sun Pharma Italia Srl

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Authors' contributions

SF contributed to protocol drafting and was a major contributor in writing the manuscript. CR and PB were major contributors in study design, protocol drafting and equally contributed to manuscript writing. All authors read and approved the final manuscript.

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Figures

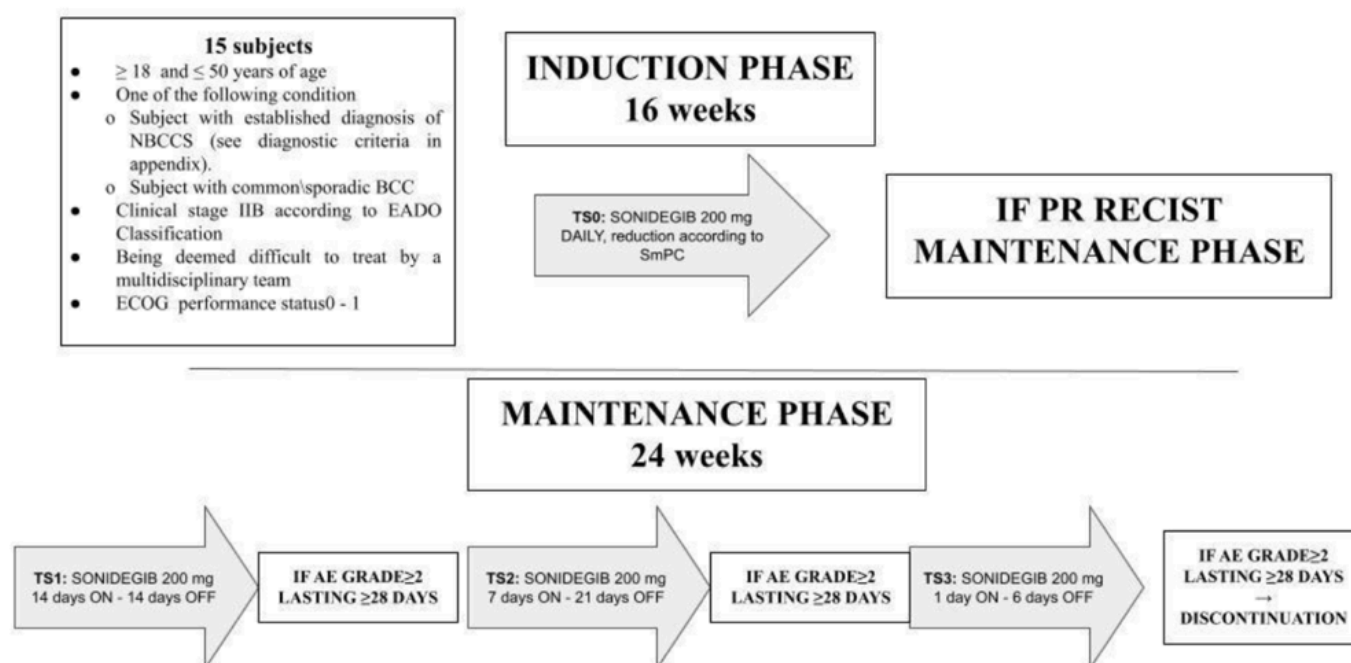


Figure 1

SIBLINGS trial's study design. (C. Resteghini, 2024)