A Phase 2, Multicenter, Open-label, Proof of-Concept Study with Safety Run-in to Evaluate the Safety, Pharmacokinetics, and Efficacy of VP-315 in Adult Subjects with Basal Cell Carcinoma

NCT05188729

Protocol Version/Date: 9.0 (Amendment 8) 13 October 2023

CLINICAL STUDY PROTOCOL

A Phase 2, Multicenter, Open-label, Proof-of-Concept Study with Safety Run-in to Evaluate the Safety, Pharmacokinetics, and Efficacy of VP-315 in Adult Subjects with Basal Cell Carcinoma

Sponsor:	Verrica Pharmaceuticals Inc. 44 West Gay Street, Suite 400 West Chester, PA 19380
Protocol Number:	VP-315-201
Phase	2
Indication:	Treatment of basal cell carcinoma
Sponsor Contact:	Cindy Willson, RN, BSN Sr. Director Clinical Operations Verrica Pharmaceuticals Inc. 44 West Gay Street, Suite 400 West Chester, PA 19380 (415) 823-4449
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Protocol Version/Date	9.0 (Amendment 8): 13 October 2023
Supersedes	8.0 (Amendment 7): 29 August 2023
Supersedes	7.0 (Amendment 6): 16 June 2023
Supersedes	6.0 (Amendment 5): 28 April 2023
Supersedes	5.0 (Amendment 4): 01 March 2023
Supersedes	4.0 (Amendment 3): 01 June 2022
Supersedes	3.0 (Amendment 2): 09 March 2022
Supersedes	2.0 (Amendment 1): 19 November 2021

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE PAGE

SPONSOR APPROVAL AND ACKNOWLEDGMENT

A Phase 2, Multicenter, Open-label, Proof-of-concept Study with Safety Run-in to Evaluate the Safety, Pharmacokinetics, and Efficacy of VP-315 in Adult Subjects with Basal Cell Carcinoma (VP-315-201)

This protocol was subject to critical review by Verrica Pharmaceuticals Inc. and has been approved by the following persons:

SPONSOR:

DocuSigned by:
Cindy Willson RN, BSN
Signer Name: Cindy Willson RN, BSN
Signing Reason: I approve this document
Signing Time: 20-Oct-2023 | 3:52:34 PM EDT
FBBB6025E10E483BBF9544ABD71DFBBB

20-Oct-2023

Cindy Willson, RN, BSN
Sr. Director of Clinical Operations
Verrica Pharmaceuticals Inc.

Date

SPONSOR MEDICAL MONITOR:

DocuSigned by:
Gary Goldenberg, MD
Signer Name: Gary Goldenberg, MD
Signing Reason: I approve this document
Signing Time: 20-Oct-2023 | 12:44:54 PM PDT
63C2E63803064DCF9696C90893FDA438

20-Oct-2023

Gary Goldenberg, MD
Chief Medical Officer
Verrica Pharmaceuticals Inc.

Date

INVESTIGATOR AGREEMENT

This protocol is the property of Verrica Pharmaceuticals Inc. I understand that the information within it is confidential and is provided to me for review by myself, my staff, and applicable ethics committees. I understand that the protocol must be kept in a confidential manner and must be returned to the sponsor (Verrica Pharmaceuticals Inc.) or destroyed per Verrica Pharmaceuticals Inc. instructions, upon request. No part of this protocol may be reproduced in any form without permission from Verrica Pharmaceuticals Inc. By accepting this protocol, I agree that the information contained herein will not be disclosed to a third party without written authorization from Verrica Pharmaceuticals Inc.

I have read and understood the protocol and agree that it contains all of the necessary information to carry out the study.

I agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the following: Good Clinical Practice (GCP) as described in International Council for Harmonisation (ICH) guideline E6(R2), and in 21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the most recent revision of the Declaration of Helsinki (October 2013) that is recognized by the US Food and Drug Administration (FDA), the European Medicines Agency, and other regulatory agencies.

I agree that I will not modify this protocol without obtaining the prior approval of the sponsor and of the institutional review board or independent ethics committee, except when necessary to protect the safety, rights, or welfare of subjects.

Investigator's Printed Name and Study Center: _____ _____

_____ _____

Signature Date

SUMMARY OF CHANGES TO THE CLINICAL PROTOCOL

VP-315-201

A Phase 2, Multicenter, Open-label, Proof-of-concept Study with Safety Run-in to Evaluate the Safety, Pharmacokinetics, and Efficacy of VP-315 in Adult Subjects with Basal Cell Carcinoma

Current Edition:	9.0 (Amendment 8)	13 October 2023
Supersedes:	8.0 (Amendment 7)	29 August 2023
	7.0 (Amendment 6)	16 June 2023
	6.0 (Amendment 5)	28 April 2023
	5.0 (Amendment 4)	01 March 2023
	4.0 (Amendment 3)	01 June 2022
	3.0 (Amendment 2)	09 March 2022
	2.0 (Amendment 1)	19 November 2021

Major Reason(s) and Rationale for Amendment:

The protocol has been amended to clarify the following items:

Part 2, Cohort 5 Expansion Group has been approved by the SRC on October 11, 2023:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 5.
- After each treatment, the additional subjects enrolled into Cohort 5: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

To provide clarification to Subject Exclusion Criteria (Section 5.3) #6. and 6. c.:

Subjects who meet <u>any</u> of the following exclusion criteria are not to be enrolled in this study.

6. Chronic medical condition such as, but not limited to:

    c. ***Subjects presenting with a systolic BP <110 mmHg and/or diastolic BP <70 mmHg at Screening or Week 1 Day 1,*** or a history of cerebrovascular or cardiac disorders, or subjects at particular risk of sequelae following a short hypotensive episode.

Changes by Section are detailed in the table that follows.

Comparative Changes

Previous Version:	**8.0 – Amendment 7 (29August 2023)**	**Current Version:**	**9.0 - Amendment 8 (13 October 2023)**

Initial Text	**Added, Deleted, or Modified Text**
GLOBAL	
Grammatical and formatting refinements to improve readability and ease of use.	
Multiple Sections	
Initial Text: …surgical excision of all target and nontarget lesions 4 to 6 weeks (Part 1) and 12 to 13 weeks (Part 2) after W1D1 injection	Modified: …surgical excision of all target and nontarget lesions 4 to 6 weeks (Part 1) and 12 to ~~13~~ **14** weeks (Part 2) after W1D1 injection
Rationale: *Modified excision time for EOT window to allow for subject scheduling flexibility.*	
4.1 Study Design	
Initial Text: Part 2 (N= 66 to 72): VP-315 once-daily dosing; will be a total daily dose of 8 mg in up to 5 cohorts (i.e, there were no DLTs that occurred during Part 1 of the study and the maximum dose of 8 mg was achieved). • **Cohort 4** (N=30 (10 initial/20 expansion): • **Cohort 5** (N=30 (10 initial/20 expansion): **…** For the first 10 subjects enrolled into Part 2 (Cohorts 4 and 5): after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous vital signs, electrocardiographic and AE monitoring). **Cohort 4 expansion group:** An SRC meeting was convened after the 10 subjects in Cohort 4 completed the Safety Assessment and approved the following: • 20 additional subjects (for a total of 30 subjects) will be enrolled into Cohort 4. • After each treatment, the additional 20 subjects enrolled into Cohort 4 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous vital signs,	Modified, Added, Deleted: Part 2 (N= **Approximately** 66 to 72): VP-315 once-daily dosing; will be a total daily dose of 8 mg in up to 5 cohorts (i.e, there were no DLTs that occurred during Part 1 of the study and the maximum dose of 8 mg was achieved). • **Cohort 4** (N= **Approximately** 30 (10 initial/**up to** 20 expansion): • **Cohort 5** (N= **Approximately** 30 (10 initial/**up to** 20 expansion): **…** For the first 10 subjects enrolled into Part 2 (Cohorts 4 and 5): after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous ~~vital signs~~ **blood pressure**, electrocardiographic and AE monitoring). **Cohort 4 expansion group:** An SRC meeting was convened after the 10 subjects in Cohort 4 completed the Safety Assessment and approved the following: • **Up to** 20 additional subjects (for a total of **approximately** 30 subjects) will be enrolled into Cohort 4. • After each treatment, the additional ~~20~~ subjects enrolled into Cohort 4 expansion: will remain in the study center for up to 1-hour (reduced from 2-

Initial Text	Added, Deleted, or Modified Text
electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI. **NOTE:** An additional SRC meeting will convene after the 10 subjects in Cohort 5 have completed the Safety Assessment Visit to review the following topics: • to review any safety signals that may have occurred that could impact further treatment • if the 2 hours of safety monitoring can be reduced to 1-hour post second injection at treatment (an additional hour may be continued at the discretion of the PI). • if enrollment can be expanded to include an additional 20 subjects for a total of 30 subjects in each cohort. If Cohort 5 is approved by the SRC for expansion; 20 additional subjects will be enrolled into Cohort 5. Four to 6 weeks in Part 1, and 12 to 13 weeks (Part 2) after the first injection of VP 315, subjects will return for all target and nontarget BCC lesions (Section 5.4) to be excised for histological evaluation.	hours) post second injection for safety monitoring (e.g., continuous ~~vital signs~~**blood pressure**, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI. **Cohort 5 expansion group:** **An SRC meeting was convened after the 10 subjects in Cohort 5 completed the Safety Assessment and approved the following:** • **Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 5.** • **After each treatment, the additional subjects enrolled into Cohort 5 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.** ~~**NOTE:** An additional SRC meeting will convene after the 10 subjects in Cohort 5 have completed the Safety Assessment Visit to review the following topics:~~ ~~• to review any safety signals that may have occurred that could impact further treatment~~ ~~• if the 2 hours of safety monitoring can be reduced to 1-hour post second injection at treatment (an additional hour may be continued at the discretion of the PI).~~ ~~• if enrollment can be expanded to include an additional 20 subjects for a total of 30 subjects in each cohort.~~ ~~If Cohort 5 is approved by the SRC for expansion; 20 additional subjects will be enrolled into Cohort 5.~~ Four to 6 weeks in Part 1, and 12 to ~~13~~**14** weeks (Part 2) after the first injection of VP 315, subjects will return for all target and nontarget BCC lesions (Section 5.4) to be excised for histological evaluation.
Rationale: *To provide clarification on the updated study design following the Part 2 Cohort 5 SRC meeting.*	
5.3 Subject Exclusion Criteria	
Initial Text: 6. Chronic medical condition that in the judgment of the investigator(s) would interfere with the performance of the study or would place the subject at undue risk, such as, but not limited to: • History of cerebrovascular or cardiac disorders, or subjects at particular risk of sequelae following a short hypotensive episode, including subjects	Modified: 6. Chronic medical condition ~~that in the judgment of the investigator(s) would interfere with the performance of the study or would place the subject at undue risk,~~ such as, but not limited to:

Initial Text	Added, Deleted, or Modified Text
with systolic BP <110 mmHg and/or diastolic BP <70 mmHg at screening or Day 1	c. ***Subjects presenting with systolic BP <110 mmHg and/or diastolic BP <70 mmHg at screening or Day 1 or W1D1*****, or a** History of cerebrovascular or cardiac disorders, or subjects at particular risk of sequelae following a short hypotensive episode**.**~~, including subjects with systolic BP <110 mmHg and/or diastolic BP <70 mmHg at screening or Day 1~~
Rationale: *To provide clarification on blood pressure exclusion criteria*	
7.3.1 Management of Postinjection Reactions to VP-315	
Initial Text: In Part 2, subjects will continue to be closely monitored for any safety signaling. If a TRAE is identified, the medical monitor will review and determine if treatment should be continued.	Modified: In Part 2, subjects will continue to be closely monitored for any safety signaling. If a TRAE **SI** is identified **(Section 10.2)**, the medical monitor will review and determine if treatment should be continued.
Rationale: *To provide additional information for AEs requiring medical monitor review.*	
7.3.2.2 Study Part 2	
Initial Text: • **Cohort 4** (N=30 (10 initial/20 expansion): • **Cohort 5** (N=30 (10 initial/20 expansion): …For the first 10 subjects enrolled into Cohorts 4 and 5: after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous vital signs, electrocardiographic and AE monitoring). • An SRC meeting will convene after the 10 subjects in each cohort (4 and 5) have completed the Safety Assessment Visit to review the following topics: o to review the safety signals that may have occurred that could impact further treatment o if the 2 hours of safety monitoring can be reduced to 1-hour post 2nd injection at treatment (an additional hour may be continued at the discretion of the PI). o if enrollment can be expanded to include an additional 20 subjects for a total of 30 subjects in each cohort. If Cohorts 4 and 5 are approved by the SRC for expansion; 20 additional subjects will be enrolled into Cohort 4 followed by 20 subjects enrolled into Cohort 5.	Modified: • **Cohort 4** (N= **Approximately** 30 (10 initial/**up to** 20 expansion): • **Cohort 5** (N= **Approximately** 30 (10 initial/**up to** 20 expansion): …For the first 10 subjects enrolled into Cohorts 4 and 5: after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous **blood pressure**~~vital signs~~, electrocardiographic and AE monitoring). **SRC Meetings** ~~An~~ **Two separate** SRC meeting**s** ~~will~~**were** convene**d** after ~~the~~ 10 subjects in each **initial** cohort (4 and 5) ~~have~~ completed the Safety Assessment Visit to review the following topics: o to review the safety signals that may have occurred that could impact further treatment o **to determine** if the 2 hours of safety monitoring **could** ~~can~~ be reduced to 1-hour post 2nd injection at treatment (an additional hour may be continued at the discretion of the PI). o **to determine** if enrollment **could** ~~can~~ be expanded to include ~~an additional~~ **up to** 20 **additional** subjects for a total of **approximately** 30 subjects in each cohort.

Initial Text	Added, Deleted, or Modified Text
Subjects may be discontinued for AEs at any time per the discretion of the investigator. Subject dosing will continue until any TRAE of any grade occurs, with the exception of Grade 1 TRAEs indicative of local reactogenicity (injection-site pain, erythema, induration). Systemic reactogenic AEs (fever, myalgia, headache) and Grade 2 local reactogenic AEs will be considered TRAEs of special interest (Section 10.2). If there is a clinically significant AE or abnormal laboratory result at the EOS visit, follow-up (F/U) visits may be required until resolution of the abnormality, or until the condition is considered clinically stable.	**The SRC approved the following for both Cohorts 4 and 5:** • **Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohorts 4 and 5 (expansion groups) respectively.** • **After each treatment, the additional subjects enrolled into Cohorts 4 and 5 expansion groups: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.** ~~If Cohorts 4 and 5 are approved by the SRC for expansion; 20 additional subjects will be enrolled into Cohort 4 followed by 20 subjects enrolled into Cohort 5.~~ ~~Subjects may be discontinued for AEs at any time per the discretion of the investigator.~~ **Management of TRAEs (see Sections 7.3.1and 10.2)** Subject dosing will continue until any TRAE of any grade occurs, with the exception of Grade 1 TRAEs indicative of local reactogenicity (injection-site pain, erythema, induration). Systemic reactogenic AEs (fever, myalgia, headache) and Grade 2 local reactogenic AEs will be considered TRAEs of special interest (Section 10.2). **If a TRAE SI is identified, the site will notify the medical monitor who will review and determine if treatment should be continued.** **For TRAE SIs occurring during VP-315 injections, or within 1-hour after the last injection, injections should stop until resolution of the reaction. If the reaction occurs during the first injection of the dose and resolves within 1-hour, the second injection of the dose may continue.** **For TRAE SIs Grade 2 (per CTCAE V5) and higher reactions, the investigator must stop further injections in accordance with TRAE SI/DLT descriptions (Section 10.2). and Tryptase must be collected per protocol (Section 8.4.5).** If there is a clinically significant AE or abnormal laboratory result at the EOS visit, follow-up (F/U) visits may be required until resolution of the abnormality, or until the condition is considered clinically stable. **All AEs including TRAE SIs should be recorded on the subject's AE Form.** **Subjects may be discontinued for AEs at any time per the discretion of the investigator.**

Initial Text	Added, Deleted, or Modified Text
Rationale: *To provide updated information on Study Part 2, Cohort 5 and Cohort 5 expansion group and management of TRAEs*	
7.4.3. Stopping Rules	
Initial Text: **Part 2 of the study**: The occurrence of a TRAE of special interest in any subject will result in discontinuation of VP-315 in that subject. In all cases, the SRC will have the authority to discontinue or modify VP-315 dosing if TRAEs, changes in vital signs, ECGs, or clinical laboratory results are observed and these changes are determined to pose a significant health risk to the subject.	Modified: **Part 2 of the study**: **For Grade 2 TRAE SIs and higher (per CTCAE V5), the investigator should discontinue VP-315 treatment, collect Tryptase per protocol (Section 8.4.5) in that subject and the subject should return for all follow-up visits.** ~~The occurrence of a TRAE of special interest in any subject will result in discontinuation of VP-315 in that subject.~~ In all cases, the SRC will have the authority to discontinue or modify VP-315 dosing if TRAEs, changes in vital signs, ECGs, or clinical laboratory results are observed and these changes are determined to pose a significant health risk to the subject.
Rationale: *To provide clarification for stopping rules in Part 2.*	
8.1 Screening Assessments	
Initial Text: Each subject must sign and date the ICF prior to their participation in any screening activities. Prospective subjects are expected to complete Screening evaluations (exclusive of biopsy) no more than 42 days prior to the planned date of the first study drug administration (Day 1).	Added: Each subject must sign and date the ICF prior to their participation in any screening activities. Prospective subjects are expected to complete Screening evaluations (exclusive of biopsy) no more than 42 days prior to the planned date of the first study drug administration (Day 1). **Note: Subjects with a systolic BP <110 mmHg and/or diastolic BP <70 mmHg at the Screening visit do not meet inclusion criteria and should not be enrolled into the study.**
Rationale: *Added a note to highlight the blood pressure requirements at the Screening visit.*	
8.2 Treatment Period	
Initial Text: After each treatment, all subjects will remain in the study center for up to 2 hours for safety monitoring (e.g., continuous vital signs, electrocardiographic and AE monitoring) and plasma PK sampling (in Part 2) as detailed in Table 8-1. After each treatment, the additional 20 subjects enrolled into Cohort 4 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous vital signs, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.	Modified: After each treatment, all subjects **in Part 1, Part 2 – Cohort 1, Cohort 2 and Cohorts 4 and 5 (first 10 subjects in each)** will remain in the study center for up to 2 hours for safety monitoring (e.g., continuous ~~vital signs~~**blood pressure**, electrocardiographic and AE monitoring) ~~and plasma PK sampling (in Part 2) as detailed in Table 8-1~~. After each treatment, the additional 20 subjects enrolled into Cohort**s** 4 **and 5** expansion **groups**: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous ~~vital signs~~**blood pressure**, electrocardiographic and AE monitoring), an additional hour may be continued at the

Initial Text	Added, Deleted, or Modified Text
	discretion of the PI. **Plasma PK sampling will be collected (in Part 2, Cohorts 4 and 5 expansion groups) as detailed in** Table 8-1.
Rationale: *To provide updated information on safety monitoring time and PK sampling.*	
Table 8-1 Schedule of Assessments - Footnotes	

Initial Text	Added, Deleted, or Modified Text
Initial Text: **Footnote c:** Vital signs (e.g., temperature, HR, BP) will be obtained at screening and at each treatment prior to application of study drug. Height and weight will be collected at Screening and EOS. Subjects must be supine for at least 5 minutes before BP and pulse rate measurements. On VP-315 dosing days, BP will be monitored serially just prior to injection, at 1, 3, and 5 minutes after each injection, and then every 5 minutes until 2 hours post last injection of the day using an automated cuff system. For subjects in Part 2 (Cohort 4 expansion group), monitoring of BP *has* been decreased to 1-hour by the SRC following their safety meetings. An additional hour may be continued at the discretion of the PI.	Modified: **Footnote c:** Vital signs (e.g., temperature, HR, BP) will be obtained at screening and at each treatment prior to application of study drug. Height and weight will be collected at Screening and EOS. Subjects must be supine for at least 5 minutes before BP and pulse rate measurements. On VP-315 dosing days, BP will be monitored serially just prior to injection, at 1, 3, and 5 minutes after each injection, and then every 5 minutes until 2 hours post last injection of the day using a~~n~~ **manual/**automated cuff system. For subjects in Part 2 (Cohort**s** 4 **and 5** expansion groups), monitoring of BP *has* been decreased to 1-hour by the SRC following their safety meeting**s**. An additional hour may be continued at the discretion of the PI.
Initial Text: **Footnote f:** Resting 12-lead ECGs (equipment provided by ECG Core Lab) will be recorded after the subject has been supine and at rest for at least 5 minutes at all visits, and prior to dosing on VP-315 dosing days. On VP-315 dosing days, 5-electrode Holter/telemetry (equipment provided by ECG Core Lab) will also be monitored continuously starting 15 minutes prior to injection and continuing 2-hours post last injection of the day. For subjects in Part 2 (Cohorts 4 expansion group), Holter/telemetry monitoring *has* been decreased to 1-hour by the SRC following their safety meeting. An additional hour may be continued at the discretion of the PI. Note, in the event of EGC Core Lab equipment failure for the 12-lead ECG, sites may use their own 12-lead ECG machine and contact the ECG Core Lab for directions regarding upload to the study portal.	Modified: **Footnote f:** Resting 12-lead ECGs (equipment provided by ECG Core Lab) will be recorded after the subject has been supine and at rest for at least 5 minutes at all visits, and prior to dosing on VP-315 dosing days. On VP-315 dosing days, 5-electrode Holter/telemetry (equipment provided by ECG Core Lab) will also be monitored continuously starting 15 minutes prior to injection and continuing 2-hours post last injection of the day. For subjects in Part 2 (Cohort**s** 4 **and 5** expansion group**s**), Holter/telemetry monitoring *has* been decreased to 1-hour by the SRC following their safety meeting**s**. An additional hour may be continued at the discretion of the PI. Note, in the event of EGC Core Lab equipment failure for the 12-lead ECG, sites may use their own 12-lead ECG machine and contact the ECG Core Lab for directions regarding upload to the study portal.
Initial Text: **Footnote t (b):** Cohorts 4-5: If only 1 target lesion is treated and complete necrosis is not achieved at the W1 Safety Assessment Visit, subjects should return on W2D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered. If a second target lesion was treated and complete necrosis is not achieved at the W2 Safety Assessment Visit, subjects should return on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered.	Modified: **Footnote t (b):** Cohorts 4-5 **(including expansion groups)**: If only 1 target lesion is treated and complete necrosis is not achieved at the W1 Safety Assessment Visit, subjects should return on W2D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered. If a second target lesion was treated and complete necrosis is not achieved at the W2 Safety Assessment Visit, subjects should return on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered.
Rationale: *To provide updated information on Cohort 5 expansion group.*	
8.4.2 Vital Signs Data	

Initial Text	Added, Deleted, or Modified Text
Initial text: On VP-315 dosing days, blood pressure will be monitored serially just prior to injection, at 1-, 3-, and 5-minutes after each injection, and then every 5-minutes until 2 hours after the last injection of the day using an automated cuff system (Table 8-1). For subjects in Part 2 – Cohort 4 expansion group, monitoring of BP has been decreased to 1-hour post treatment (an additional hour may be continued at the discretion of the PI).	Modified: On VP-315 dosing days, blood pressure will be monitored serially **(observing for hypotension that meets the definitions as described in Section 10.2)**: just prior to injection, at 1-, 3-, and 5-minutes after each injection, and then every 5-minutes until 2 hours after the last injection of the day using a **manual/**~~n~~-automated cuff system (Table 8-1). For subjects in Part 2 – Cohort**s** 4 **and 5** expansion group**s**, monitoring of BP has been decreased to 1-hour post treatment (an additional hour may be continued at the discretion of the PI).
Rationale: *To provide updated information on the reduction in time for post treatment monitoring of blood pressure.*	
8.4.3 Electrocardiograms	
Initial text: …..For subjects in Part 2 Cohort 4 expansion group, Holter/telemetry has been decreased to 1-hour after the last injection of the day after receipt of the second daily dose of VP-315 (an additional hour may be continued at the discretion of the PI).	Modified: …..For subjects in Part 2 Cohort**s** 4 **and 5** expansion group**s**, Holter/telemetry has been decreased to 1-hour after the last injection of the day after receipt of the second daily dose of VP-315 (an additional hour may be continued at the discretion of the PI).
Rationale: *To provide updated information on the reduction in time for post injection cardiac monitoring.*	
8.4.4 Clinical Laboratory Testing	
Initial text: A Clinical Laboratory Improvement Amendments certified laboratory will perform the clinical laboratory tests for this study as scheduled in Table 8-1. Tests are listed in Table 8-2 and will be performed at Screening, at each Safety Assessment Visit, at Unscheduled Visits and at the EOS; for subjects with excised lesions on both the face and the body, clinical laboratory samples will be collected only at the second EOS visit (i.e, at the EOS for Body)**.** Clinical laboratory testing for hematology, serum chemistry, pregnancy tests, and tryptase levels will be performed in the local clinical laboratories at the study site.	Modified: A Clinical Laboratory Improvement Amendments **(CLIA)** certified laboratory **[either central or local]** will perform the clinical laboratory tests for this study as scheduled in Table 8-1. Tests are listed in Table 8-2 and will be performed at Screening, at each Safety Assessment Visit, at Unscheduled Visits and at the EOS; for subjects with excised lesions on both the face and the body, clinical laboratory samples will be collected only at the second EOS visit (i.e, at the EOS for Body)**.** ~~Clinical laboratory testing for hematology, serum chemistry, pregnancy tests, and tryptase levels will be performed in the local clinical laboratories at the study site.~~
Rationale: *Updated information to include central laboratory*	
Table 8-2 Clinical Laboratory Tests	
Initial text:	Added: **T-Cell Clonality (Central lab only)** **Expansion Cohorts 4 and 5**

Initial Text	Added, Deleted, or Modified Text
	Serum Pharmacokinetics (PK) [Central lab only]
Rationale: *To provide information on the central lab specimens.*	
8.4.5 Serum Tryptase Assessment	
Initial text: … The actual collection time must be recorded entered into the subject's record/source documents and transcribed to the CRFaccordingly.	Modified: … The actual collection time must be ~~recorded~~**entered** in**to** the subject's **record/**source ~~documents~~ and transcribed ~~to the CRF~~**accordingly**.
Rationale: *To provide clarity for appropriate documentation.*	
8.4.8 Pharmacokinetic Assessments	
Initial text: • Additional samples will be collected on the ***following day 24 hours (±1 hour) post prior injection*** of VP-315.	Modified: • Additional samples will be collected on the ***following day 24 hours (±1 hour) post*** ~~***prior***~~***Day 1 first injection*** of VP-315 ***(prior to Day 2 injection)***.
Rationale: *To provide clarification for timing of PK samples.*	
8.5.1 Lesion Evaluation	
Initial text: …All specimens (including *HISTORICAL* samples) will be sent as slides to the central dermatopathologist for confirmation of eligibility. In accordance with the procedures noted in Table 8-1, all target and nontarget BCC lesions will be surgically excised with a 3 mm- margin 4 to 6 weeks (Part 1) and 12 to 13 weeks (Part 2) after receipt of the W1D1 injection; slides will be sent to the central dermatopathologist for analysis/histology. If a lesion has clinically cleared, the area where the lesion was will be excised accordingly.	Modified: …All specimens (including *HISTORICAL* samples) will be **formalin-fixed and paraffin embedded (FFPE) and H&E stained slides of specimen slices will be prepared and reviewed locally to determine** ~~sent as slides to the central dermatopathologist for confirmation of~~ eligibility. **The H&E stained slides will be sent to the central lab for imaging and high quality images of the slides will be sent to the central dermatopathologist for confirmation of analysis/histology.**

Initial Text	Added, Deleted, or Modified Text
	In accordance with the procedures noted in Table 8-1, all target and nontarget BCC lesions will be surgically excised with a 3 mm- margin 4 to 6 weeks (Part 1) and 12 to ~~13~~**14** weeks (Part 2) after receipt of the W1D1 injection **and tissue specimens preserved by FFPE. If a lesion has clinically cleared, the area where the lesion was will be excised accordingly. Both the screening and post-excision tissue blocks will be sent to the central lab for analysis of immune activation biomarkers including TILs by multiplexed IF-IHC, as well as for sequencing of genomic DNA from the lesion specimens to assess changes in T-cell receptor clonality.** ~~; slides will be sent to the central dermatopathologist for analysis/histology. If a lesion has clinically cleared, the area where the lesion was will be excised accordingly.~~
Rationale: *To provide updated central lab information on the process for BCC tissue samples and analysis.*	
8.8 Assessment of the Immunological Response to VP-315 Treatment	
Initial text: In a subset of subjects, the anti-tumor immunological response to VP-315 treatment will be assessed in the excised tissue obtained from basal cell tumor biopsies performed at pre-screening (baseline) and at the approximate 12-week post-treatment visit, as well as in peripheral blood samples acquired at the same time points.	Modified: In a subset of subjects, the anti-tumor immunological response to VP-315 treatment will be assessed in the excised tissue obtained from basal cell tumor biopsies performed at pre-screening (baseline) and at the approximate 12 to **14**-week post-treatment visit, as well as in peripheral blood samples acquired at the same time points.
Rationale: *To include the window of the post-treatment visit.*	
10.2 Dose-limiting Toxicity/Treatment-related Adverse Event of Special Interest	
Initial text: In Part 1, any subject who experiences a DLT/**TRAE SI** will receive no further VP-315. If the DLT is caused by an unexpected drug-related event that is not listed in the consent form, Sponsor will revise the consent form appropriately and submit it to the IRB.	Modified: ~~In Part 1, any~~ **Any** subject who experiences a DLT**/TRAE SI** will receive no further VP-315. If the DLT**/TRAE SI** is caused by an unexpected drug-related event that is not listed in the consent form, Sponsor will revise the consent form appropriately and submit it to the IRB.
Rationale: *To provide clarification with TRAE SI.*	

1. PROTOCOL SYNOPSIS

Protocol Title: A Phase 2, Multicenter, Open-label, Proof-of-Concept Study with Safety Run-in to Evaluate the Safety, Pharmacokinetics, and Efficacy of VP-315 in Adult Subjects with Basal Cell Carcinoma

Phase: 2

Indication: basal cell carcinoma (BCC)

Hypotheses, Objectives, and Endpoints:

There is no formal hypothesis testing in this study. The following objectives and associated endpoints will be evaluated in this 2-part study:

Part 1	
Primary Objectives	**Endpoints**
• To assess the safety, tolerability, and maximum tolerated dose (MTD) of ascending dose strengths of VP-315	• Discontinuations due to adverse events (Aes); occurrence of dose-limiting toxicities (DLTs) • Cutaneous Reaction Assessment (CRA)
Exploratory Objectives	**Endpoints**
• To evaluate the objective antitumor efficacy of VP-315	• Histological clearance of treated lesion(s) at excision • Clinical clearance of treated lesion(s) as determined by visual assessment (no tumor seen upon visible inspection) at excision • Estimate of remaining tumor volume (necrotic cells:tumor cells) at excision • Abscopal effect as determined by clinical and histological clearance of nontreated lesions at excision • Physician Global Assessment (PGA)
Part 2 (Cohorts 1 and 2)	
Primary Objectives	**Endpoints**
• To determine the optimal regimen for dosing 8 mg of VP-315 based on safety and tolerability	• Treatment-related Aes; treatment-related serious adverse events (SAEs); discontinuations due to Aes; occurrence of TRAEs of special interest • CRA

Secondary Objectives	**Endpoints**
• To evaluate the antitumor efficacy of VP-315	• Clinical clearance of treated lesion at excision as determined by visual assessment (no residual tumor seen on visual inspection) • Histological clearance of treated lesion(s) at excision • Abscopal effect as determined by clinical and histological clearance of nontreated lesions at excision if nontreated lesions exist • Estimate of remaining tumor volume (necrotic cells:tumor cells) at excision • PGA
Exploratory Objectives	**Endpoints**
• To assess the immune response to VP-315 treatment in a subset of subjects by assessing the immune repertoire in blood and in tissue	• Multiplex immunohistochemical staining for T-cell subsets and immune activation markers in tumor tissue samples • Analysis of T-cell clonality in blood and tumor tissue samples
• To assess subject satisfaction with the treatment	• SCAR-Q, FACE-Q
Part 2 (Cohorts 4 and 5)	
Primary Objectives	**Endpoints**
• To gain additional information on the safety, tolerability, and dosing regimen of VP-315 to support a pivotal study protocol design	• Treatment-related Aes; treatment-related serious adverse events (SAEs); discontinuations due to Aes; occurrence of TRAEs of special interest • CRA
Secondary Objectives	**Endpoints**
• To confirm the antitumor efficacy of VP-315 using the optimal dosing regimen determined in Part 2	• Clinical clearance of treated lesion at excision as determined by visual assessment (no residual tumor seen on visual inspection) • Histological clearance of treated lesion(s) at excision • Abscopal effect as determined by clinical and histological clearance of nontreated lesions at excision if nontreated lesions exist • Estimate of remaining tumor volume (necrotic cells:tumor cells) at excision • PGA

• To characterize the pharmacokinetics (PK) of an 8 mg dose of VP-315 administered with the optimal dosing regimen determined in Part 2.	• Plasma VP-315 concentrations
Exploratory Objectives	**Endpoints**
• To assess subject and physician satisfaction with the treatment	• SCAR-Q, FACE-Q, • Scar Cosmesis Assessment and Rating (SCAR) Scale
• To assess the immune response to VP-315 treatment in a subset of subjects by assessing the immune repertoire in blood and in tissue	• Multiplex immunohistochemical staining for T-cell subset and immune activation markers in tumor tissue samples • Analysis of T-cell clonality in blood and tumor tissue samples

Study Design: This is an open-label, multicenter, proof-of-concept study with a safety run-in designed to assess the safety, tolerability, MTD, and objective antitumor efficacy of VP-315 when administered intratumorally to adults with biopsy-proven BCC.

This study is expected to enroll approximately 80 subjects with a histological diagnosis of BCC in at least 1 eligible target lesion (confirmed by punch or shave biopsy).

This is a 2-part study with sequential enrollment. All enrolled subjects will receive VP-315 intratumoral injection on an outpatient basis into up to 2 target lesions:

Part 1 (N= 2 to 8): VP- 315 once-daily dosing; starting total daily dose of 2 mg for the first subject. Ascending once-daily 1-mg dosing increments (e.g., 2 mg on Day 1, 3 mg on Day 2). Subjects may be treated for a maximum of 2 weeks and a maximum total daily dose of 8 mg in Part 1. The starting dose will be escalated between subject cohorts in 1-mg increments after the previous cohort has completed Week 1 dosing (the DLT observation period) (Figure 7-1 and Figure 7-2).

Part 2 (N= Approximately 66 to 72):VP-315 once-daily dosing; will be a total daily dose of 8 mg in up to 5 cohorts (i.e. there were no DLTs that occurred during Part 1 and the maximum dose of 8 mg was achieved).

- **Cohort 1** (N=3-6): VP-315 once-daily dosing of 8 mg with a loading dose of half the target dose of 8 mg (i.e. 4 mg) only on W1D1; all remaining doses will be the full target dose without a loading dose. Subjects will be treated until the lesion is necrosed, for a maximum of 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3 – up to 6 total doses).

Cohort 2 (N=3-6): VP-315 once-daily dosing of 8 mg on all treatment days (i.e., NO LOADING dose on W1D1) for up to 3 consecutive daily doses/week until the lesion is necrosed, for a maximum of 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3 – up to 6 total doses).

The study design and dosing strategy listed below for Cohorts 3, 4 and 5 are recommendations from the Safety Review Committee following an adhoc safety review meeting held on June 13-14, 2023 to discuss subjects reports of pain and burning at the injection site that were not observed in Part 1 of the study:

- Recommendation: Remove/skip Cohort 3 in Part 2 of the protocol and advance from Cohort 2 to Cohorts 4 and 5. Revert to Part 1 dosing strategy of a 30/70 split dose for all treatments with the injections 19dministered 15-minutes apart.

    - *Cohort 3* (N=0)This cohort has been removed at the recommendation of the SRC. : This cohort has been removed upon the completion of Cohort 2.

For Part 2 (Cohorts 4 and 5) the highest total daily dose of VP-315 (8.0 mg) will be divided into a split dose; the first dose is not to exceed 2.4 mg (30% of 8-mg dose), and the remaining dose will not exceed 5.6 mg (70% of 8-mg dose) and administered 15 minutes apart (not to exceed 30 minutes).

- **Cohort 4** (N=Approximately 30 [10 initial/up to 20 expansion]): (Two times weekly dosing) VP-315 once-daily dosing of 8 mg, administered on 2 consecutive days in one week (W1D1, W1D2). The planned dosing regimen will be a split dose of VP-315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second Target Lesion may begin on D1 of the next week (W2D1, W2D2). Each individual target lesion is treated for the assigned 2 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 4 total doses**.
- **Cohort 5** (N=Approximately 30 [10 initial/up to 20 expansion]): (Three times weekly dosing) VP-315 once-daily dosing of 8 mg, administered on 3 consecutive days in one week (W1D1, W1D2, W1D3). The planned dosing regimen will be a split dose of VP-315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second target lesion may begin on D1 of the next week (W2D1, W2D2, W2D3). Each individual target lesion is treated for the assigned 3 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 6 total doses**.

  See (Table 7-1)

In Part 1 of the study, each 7-day treatment week comprises up to 3 consecutive treatment days followed by a no-treatment period of at least 4 days. In Part 2 of the study, each 7-day

treatment week comprises up to 2 or 3 consecutive treatment days followed by a no-treatment period of at least 4 days. Dosing will commence in a single target lesion. In Part 1 and Part 2 Cohorts 1and 2, once a target lesion has necrosed, treatment of that lesion stops, and treatment of a subsequent target lesion (up to 2 total, including the original target lesion) may continue on Day 1 of the following week. In Part 2 Cohorts 4 and 5 , treatment of a second target lesion begins on W2D1 (not based on status of necrosis of target lesion 1).

For the first 10 subjects enrolled into Cohorts 4 and 5: after each treatment, subjects will remain in the study center for up to 2-hours post second injection for safety monitoring (e.g., continuousblood pressure, electrocardiographic and AE monitoring).

Following the final treatment of the 10th subject in Cohort 4, enrollment into Cohort 5 may be initiated for 10 subjects.

Cohort 4 expansion group:

An SRC meeting was convened after the 10 subjects in Cohort 4 completed the Safety Assessment and approved the following:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 4.
- After each treatment, the additional subjects enrolled into Cohort 4 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuousblood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

Cohort 5 expansion group:

An SRC meeting was convened after the 10 subjects in Cohort 5 completed the Safety Assessment and approved the following:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 5.
- After each treatment, the additional subjects enrolled into Cohort 5 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

Plasma PK sampling will be collected in subjects in Cohorts 4 and 5 expansion groups as detailed in Table 8-1.

Planned Sample Size: Approximately 80 subjects (Part 1: approximately 2 to 8 subjects; Part 2: approximately 66 to 72 subjects enrolled at up to 15 sites in the United States (US).

Duration of Treatment: The Sponsor estimates that the study will require approximately 17 months from the time that the first subject provides signed informed consent through the last subject's last study-related visit (up to 42 days Screening; treatment in 1-week intervals until visual confirmation of necrosis of target lesions; surgical excision of all target and nontarget lesions 4 to 6 weeks (Part 1) and 12 to 14 weeks after W1D1 injection; follow-up (F/U) visit at 1- or 2-weeks post excision).

Duration of participation for an individual subject will depend on assessments of disease and tolerability of VP-315, as well as other factors. No subject will be treated for more than 2 weeks. All lesions will be excised 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after the W1D1 injection.

Key Subject Eligibility Criteria: Screening: Adults ≥18 years of age who have clinically suspected low-risk BCC with at least 1 eligible lesion suitable for biopsy and excision. Additionally, to be eligible for participation in the study, subjects are required to have a histological diagnosis of BCC in at least 1 eligible target lesion (confirmed by punch or shave biopsy) that is suitable for biopsy and excision; all lesion(s) enrolled in the study (target and non-target) must be ≥0.5 cm, and ≤2.0 cm in the longest diameter, may not be recurrent or previously treated, and must not be within 1 cm of the eyelids or lips, or on the hands, ears, nose, or genitalia.

Test Product, Dose, and Route of Administration: VP-315 comprises a de novo designed oncolytic peptide provided as LTX-315 Acetate 20 mg/vial lyophilized powder for injection that can be reconstituted in saline to a concentration ranging from 4 to 16 mg/mL. VP-315 will be administered via intradermal injection into a single target lesion. In all parts of the study, the targeted total volume of delivery is 500 µL daily. In Part 1, the 500-uL dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Part 2 (Cohorts 1 and 2) will determine the optimal dosing regimen for an 8mg dose based on safety, tolerability, and biological response to VP-315. This optimal dosing regimen will be used in Part 2 (Cohorts 4 and 5).

Reference Product, Dose, and Route of Administration: None.

Statistical Considerations: No formal inferential statistical analyses will be performed. Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables. Results will be presented by study period. Data will be presented for all subjects in listings.

An accounting of the study subjects by disposition will be tabulated. Demographic data (e.g., age, gender, and race), medical history, cancer history, and other baseline characteristics will be summarized.

Safety Evaluation: The general safety and tolerability of VP-315 will be assessed using the following safety endpoints: AEs, DLTs (Part1), TRAE SIs (Part 2), CRAs, routine clinical laboratory evaluations (serum chemistry, hematology), serum tryptase levels, vital signs, electrocardiograms (ECGs) and physical examination. The incidence (%) of all treatment emergent adverse events (TEAEs) will be summarized by body system and preferred term.

Incidence rates of TEAEs will also be presented by severity and relatedness to study medication. Changes from baseline in vital signs, ECGs and laboratory values will be summarized.

Efficacy Evaluation: Efficacy will be assessed using the following efficacy endpoints: clinical clearance, histological clearance, complete clearance, tumor volume estimate, abscopal effect, and Physician's Global Assessment. The number and percentage of lesions in each category will be tabulated overall. The number and percent of lesions that achieve histological clearance will be displayed. The same analysis will be repeated for the number of lesions that achieve clinical clearance. Tumor volume estimates will be summarized using descriptive statistics.

Exploratory Evaluation: In Part 2 of the study, the immune response to VP-315 treatment will be evaluated in a subset of subjects. Tumor tissue samples from the pre-treatment screening biopsies and from the post-treatment excised tumor tissue will undergo multiplexed IF-IHC and changes in the expression of a panel of 8 immune markers in response to the treatment will be analyzed. Additionally, genomic DNA will be isolated from the same tissue samples, as well as well as from peripheral blood samples collected at the same pre- and post-treatment time points and will undergo sequencing and analyzed for changes in T-cell receptor clonality.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition/Explanation
AE	adverse event
BCC	basal cell carcinoma
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CRA	Cutaneous Reaction Assessment - *also* - clinical research associate
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	end of study (visit)
EOT	end of treatment (visit)
ET	early termination (visit)
F/U	follow-up (visit)
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gDNA	Genomic deoxyribonucleic acid
hCG	beta human chorionic gonadotropin
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
MMS	Mohs micrographic surgery

Abbreviation or Term	Definition/Explanation
MTD	maximum tolerated dose
NCI	National Cancer Institute
NMSC	nonmelanoma skin cancer
NOAEL	no observable adverse effect level(s)
Nontarget Lesion	BCC lesion to be observed for abscopal effect
Nontreated Lesion	Target lesion that was not treated with VP-315
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PPS	per-protocol analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SCAR	The Scar Cosmesis Assessment and Rating (SCAR) Scale
SCAR-Q	Scar Cosmesis Assessment and Rating Questionnaire
SRC	Safety Review Committee
Target Lesion	BCC lesion identified for treatment
Treated Lesion	Target lesion that was treated with VP-315
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TRAE SI	treatment-related adverse event of special interest
US	United States
W1D1	Week 1/Day 1
WFI	water for injection

2. BACKGROUND AND RATIONALE

2.1 Disease

Skin cancer is the most commonly diagnosed cancer in the United States (US), with nonmelanoma skin cancer (NMSC) being the most common malignancy in the US [Karimkhani, 2015] [Madan, 2010]. National incidence estimates based on the most recent year that new statistics were available (2012) estimated more than 5.4 million cases of NMSC were treated in more than 3.3 million people in the US, exceeding the number of all other cases of human malignancies combined [Rogers, 2015; AAD, 2020; Skin Cancer Foundation, 2021]. Data from the Medical Expenditure Panel Survey estimated an annual increase in treatment for NMSC (2002 to 2011) in US adults from 3.1 to 4.3 million [Guy, 2015].

Current estimates show that the approximately 80% of NMSC cases occur in people ≥60 years of age, and that the number of cases in this population could increase by an estimated 50% by 2030, illustrating the significant worldwide healthcare burden of NMSC, particularly in light-skinned populations [Diffey, 2005] [Karimkhani, 2015]. Similar increases in basal cell carcinoma (BCC) incidence rates have been shown in other studies [Sveinbjørnsson, 2017] [Wu, 2013] [Goldenberg, 2016] [Adalsteinsson, 2020].

While skin cancers have a low mortality, the average annual total cost for skin cancer increased from 2006 to 2011 by 126.2%, from $3.6 billion to $8.1 billion [Guy, 2015].

Surgery is the most common treatment for BCC and includes procedures such as excision, curettage and electrodesiccation, and Mohs micrographic surgery (MMS). Both excision and curettage leave scarring of the treatment area; MMS aims to reduce scarring, particularly in treatment areas near the eye or other areas of the face, but is a complex, protracted surgery requiring specialized training.

2.2 LTX-315

LTX-315 is a de novo designed oncolytic peptide being developed as a chemotherapeutic. LTX-315 is generated from the host-defense peptide lactoferricin. Host-defense peptides are present in almost every life form and are an integrated part of the eukaryotic immune system mounting a first-line defense against pathogens. These peptides can have both a direct killing activity and immunomodulatory properties [Hancock, 2001]. Several cationic host-defense peptides have shown anticancer activity due to their ability to bind to negatively charged membrane components on cells via electrostatic interactions [Zasloff, 2002] [Papo, 2005]. Extensive structure-activity relationship studies on peptides derived from the host-defense peptide lactoferricin has enabled the de novo design of LTX-315, in which the features important to oncolytic activity have been optimized.

LTX-315 was designed to enhance the cytolytic activity of naturally occurring host-defense peptides, subsequently inducing lysis and cell death at high local concentration [Forveille, 2015]. LTX-315 induces immunogenic cell death, killing the cells in a manner that activates the adaptive immune system. A tumor-specific immune response is activated due to an effective release of potent immune stimulants (i.e, danger signals) and a broad

repertoire of tumor antigens [Sveinbjørnsson, 2017] [Jebsen, 2019] [Liao, 2019] [Nestvold, 2017] [Camilio, 2014] [Spicer, 2021].

LTX-315 is in development by Lytix Biopharma AS as a potential anticancer agent for treatment of malignancies where at least 1 lesion is available for local injection; to date, 3 clinical trials in subjects with end-stage cancer have been concluded. A trial that has recently completed enrollment (NCT03725605) is evaluating LTX-315 induction of T-cell infiltration in patients with advanced/metastatic soft tissue sarcoma, and a trial evaluating LTX-315 in combination with pembrolizumab in patients with percutaneously accessible advanced solid tumors (NCT04796194) is currently enrolling.

Verrica is developing LTX-315 for dermatologic oncology indications with the first target indication being BCC under the name VP-315.

Additional information on preclinical studies may be found in the Investigator's Brochure.

2.2.1 Nonclinical Pharmacology

The nonclinical pharmacology data obtained for the oncolytic peptide LTX-315 supports its use as a locally injected agent for the treatment of solid tumors. LTX-315 has shown potent activity against multiple cancer cell lines, and pharmacodynamic studies of intratumoral injections have demonstrated prolonged local antitumor effects of complete response and transfer of protection from treated to untreated mice.

2.2.2 Nonclinical Toxicology and Safety

LTX-315 was designed to be administered to tumors accessible for injection in the clinic. A cyclical regimen was used to cover repeat dosing. Although no observable adverse effect levels (NOAELs) could be determined due to the pharmacological action of the compound, these studies generated data that assisted in the selection of a tolerable clinical starting dose.

Based on observations in rats and dogs, an acute reduction in mean arterial pressure was observed after intravenous (IV) administration and likely resulted from vasodilation in peripheral circulation with a decrease in total vascular resistance and was not considered to be a direct cardiac effect. In vitro studies evidenced that this transient hemodynamic effect may be caused by interaction between LTX-315 and the MRGX2 receptor on mast cells affecting peripheral blood pressure (BP) by histamine release.

2.2.3 Preclinical Pharmacokinetic Drug Interactions

The inhibitory effect of LTX-315, at concentrations up to 100 µM, on the catalytic activity of the 9 major human CYP450 isozymes was investigated in vitro using pooled human liver microsomes and isozyme-specific probe substrates [R315-24]. The inhibition profile of LTX-315 was assessed using both a 5- and 30-minute preincubation period to ascertain whether any inhibition observed was reversible (direct competitive) or irreversible (mechanism-based or time-dependent). LTX-315 caused direct inhibition of all CYP450 isozymes to some extent with IC_{50} values ranging from approximately 7 to 38 µM. The most marked inhibition was observed with CYPs 2A6, 2C8, 2C9, and 3A4 (testosterone) where IC_{50} values were all between 7 and 10 µM. There was little or no evidence for irreversible

CYP450 inhibition following a 30-minute preincubation. The greatest reduction in IC_{50} was observed with CYP2B6, where IC_{50} values of 28 and 19 μM, following a 5- or 30-minute preincubation respectively, indicating that some mild time-dependent inhibition was a possibility. In many cases, the IC_{50} increased following 30 minutes preincubation, suggesting either instability of LTX-315 in the incubation conditions, or metabolism to a less inhibitory metabolite. Based upon these results, it is considered unlikely that LTX-315 would participate in, or contribute to, inhibitory drug-drug interactions in vivo which are mediated by CYP450-dependent metabolism.

2.2.4 Toxicology

The maximum tolerated IV dose was 2 mg/kg in the rat (equivalent to a human dose of 0.324 mg/kg) and was limited by the local reaction at the injection site. In the dog, the maximum tolerated IV dose was considered to be 1.25 mg/kg based on vital clinical signs. The maximum tolerated concentration of LTX-315 in normal skin was determined to be 5 mg/mL in the rat and 10 mg/mL in dog, with maximum dose volumes of approximately 0.75 mL/injection site in rat (3 mL/kg) and approximately 2.5 mL/injection site in dog (0.25 mL/kg).

2.2.5 Summary of Clinical Experience

LTX-315 has not previously been evaluated in BCC. Two Phase 1 studies have been concluded (C08-315-01, C09-315-02 as well as a Phase I/II (C12-315-03); these studies evaluated the efficacy, safety, and pharmacokinetics (PK) of LTX-315 injection at varying dose strengths in subjects with tumors accessible for percutaneous injection, including those located in cutaneous, subcutaneous, oral regions, and in lymph nodes. Overall, the antitumor activity (tumor necrosis) of LTX-315 was observed in a number of subjects, showing marked tumor regression in both the injected and noninjected lesions. The immune analysis of tissue samples (C12-315-03) clearly demonstrated that LTX-315 has the ability to invoke necrosis, stimulate clonal T-cell expansion, and increase the repertoire of activated and targeted T cells, both within the injected tumors and in the peripheral blood [Spicer, 2021].

The most frequently reported adverse events (AEs) in these initial clinical studies were hypersensitivity related reactions that included flushing, fatigue, hypersensitivity, and injection-site swelling, particularly when LTX-315 was administered at dosages above 8 mg as a single injection. In subjects with cutaneous, subcutaneous, oral, or lymph node lesions, including highly vascularized locally advanced or metastatic tumors, hypersensitivity-related AEs leading to discontinuation were noted. Discontinuations in response to hypersensitivity-related AEs, however, were eliminated following amendment of the study protocols to reduce the maximum dose to 5 mg per injection and to limit the duration of treatment to 3 weeks.

Additional information on clinical studies may be found in the Investigator's Brochure.

2.3 Rationale

2.3.1 Rationale for the Dose Selection

The starting dose of VP-315 for this study was selected based on IND-directed toxicity studies and on experience gained from previous clinical studies of LTX-315 in adults with solid tumors. Although no NOAEL could be determined in toxicology studies due to the pharmacological action of the compound, these studies have generated data which assist in the selection of a tolerable clinical starting dose.

In the Phase 1 monotherapy dose-escalation study (C08-315-01), 14 subjects received injections of intratumoral LTX-315 at doses ranging from 1.4 mg to 9.0 mg on Day 1. Grade 2 AEs were not noted at doses below 4.0 mg on Day 1, a determinative factor in the proposed LTX-315 starting total daily dose of 2.0 mg in the current study. Additionally, BCC lesions are expected to be less vascularized than the malignancies injected to date, which is also expected to further reduce systemic effects.

In C08-315-01, at LTX-315 doses below 4.0 mg, the AEs occurring on Day 1 had a short duration (minutes), and at all doses became less severe and of shorter duration with additional LTX-315 exposure. Similarly, preclinical testing (IV administration in rats) indicates that LTX-315–related hypotension is a result of a direct effect on peripheral vasculature (without any central cardiac effect) and exhibits a tachyphylaxis effect (i.e., the largest reduction in BP occurs following the first LTX-315 dose; subsequent identical LTX-315 doses resulted in diminished BP reductions). For these reasons, the proposed total daily dose of VP-315 will be administered in 2 injections, with the initial 30% (150 µL) of the VP-315 dose being administered in the first injection, and the remaining 70% (350 µL) administered at least 15 minutes and no more than 30 minutes later. In all parts of the study, the targeted total volume of delivery is 500 µL daily. The Safety Review Committee (SRC; see Section 7.4.1) may determine in Part 2 to explore a lower volume of delivery at 250 µL daily at doses at or below 5.0 mg delivered as 75 µL in the first dose and 175 µL in the second dose.

For Part 1 of this study, the highest proposed total daily dose of VP-315(8.0 mg), is broken into two administrations at least 15 minutes apart (not to exceed 30 minutes), with the first dose not to exceed 2.4 mg (30% of 8-mg dose), and the remaining dose will not exceed 5.6 mg (70% of 8-mg dose); both doses are well below the historical 8 mg maximum tolerated dose (MTD). Therefore, the maximum dose of VP-315 in the proposed study (8.0 mg) and maximum concentration (16.0 mg/mL) should be well within the safety limits established in the previous Phase 1 monotherapy study.

For Part 2 (Cohorts 4 and 5) the highest total daily dose of VP-315 (8.0 mg) will be divided into a split dose; the first dose is not to exceed 2.4 mg (30% of 8-mg dose), and the remaining dose will not exceed 5.6 mg (70% of 8-mg dose) and administered 15 minutes apart (not to exceed 30 minutes). This dosing strategy was selected as a recommendation from the Safety Review Committee following an adhoc safety review meeting held on June 13-14, 2023 to discuss subjects reports of pain and burning at the injection site that were not observed in Part 1 of the study:

- Remove/skip Cohort 3 in Part 2 of the protocol and advance from Cohort 2 to Cohorts 4 and 5. Revert to Part 1 dosing strategy of a 30/70 split dose with the injections adminstered 15-minutes apart.

2.3.2 Rationale for the Study Design

LTX-315 has not previously been evaluated in BCC. While the dose has been established for malignant tumors, a safe and efficacious dose has not been established in otherwise healthy subjects, for whom the alternative treatment for BCC would be surgical excision. Therefore, a safety run-in to confirm the appropriate dose range will be conducted as part of the current study.

The current study comprises 2 parts. Part 1 is designed to explore the initial VP-315 safety profile when administered in escalating doses to individual subjects with BCC, starting at 2 mg and ending at a maximum of 8 mg total daily dose to a single lesion. This strategy is intended to quickly assess the MTD and gain preliminary assessment of VP-315 induction of clinical and histological necrosis of each treated lesion while seeking to establish an AE profile for BCC. Centralized photography and Cutaneous Reaction Assessment (CRA) by the investigator will be used to document BCC response to VP-315.

During Part 1 of the study, no DLTs were reported, and escalation up to 8 mg total daily dose (the maximum dose for this study) was achieved. Therefore, Part 2 is designed to determine the optimal dosing regimen using 8 mg of VP-315 identified in Part 1 and confirm the optimal dosing regimen determined from Cohorts 4 and 5 to be used in the pivitol trial.

Pharmacokinetic data will be collected to characterize the PK of an 8 mg dose of VP-315 administered with the optimal dosing regimen in Part 2 (Cohorts 4 and 5 expansion group).

3. OBJECTIVES

In this 2-part study, the following objectives and endpoints will be evaluated when administered intratumorally to adult subjects ≥18 years of age with biopsy-proven BCC:

Part 1	
Primary Objectives	**Endpoints**
• To assess the safety, tolerability, and MTD of ascending dose strengths of VP-315	• Discontinuations due to AEs; occurrence of DLTs • CRA
Exploratory Objectives	**Endpoints**
• To evaluate the objective antitumor efficacy of VP-315	• Histological clearance of treated lesion(s) at excision • Clinical clearance of treated lesion(s) at excision as determined by visual assessment (no tumor seen upon visible inspection) • Estimate of remaining tumor volume (necrotic cells:tumor cells) at excision • Abscopal effect as determined by clinical and histological clearance of nontreated lesions at excision • PGA
Part 2 (Cohorts 1 and 2)	
Primary Objectives	**Endpoints**
• To determine the optimal regimen for dosing 8 mg of VP-315 based on safety and tolerability	• Treatment-related AEs; treatment-related serious adverse events (SAEs); discontinuations due to AEs; occurrence of TRAEs of special interest • CRA
Secondary Objectives	**Endpoints**
• To evaluate the antitumor efficacy of VP-315	• Clinical clearance of treated lesion at excision as determined by visual assessment (no residual tumor seen on visual inspection) • Histological clearance of target lesion(s) at excision • Abscopal effect as determined by clinical and histological clearance of non-target lesions at excision • Estimate of remaining tumor volume (necrotic cells:tumor cells) at excision • PGA

Exploratory Objectives	**Endpoints**
• To assess the immune response to VP-315 treatment in a subset of subjects by assessing the immune repertoire in blood and in tissue	• Multiplex immunohistochemical staining for T-cell subsets and immune activation markers in tumor tissue sample • Analysis of T-cell clonality in blood and tumor tissue samples
• To assess subject satisfaction with the treatment	• SCAR-Q, FACE-Q
Part 2 (Cohorts 4 and 5)	
Primary Objectives	**Endpoints**
• To gain additional information on the safety, tolerability and dosing regimen of VP-315 to support a pivotal study protocol design	• Treatment-related AEs; treatment-related serious adverse events (SAEs); discontinuations due to AEs; occurrence of TRAEs of special interest • CRA
Secondary Objectives	**Endpoints**
• To confirm the antitumor efficacy of VP-315 using the optimal dosing regimen determined in Part 2	• Clinical clearance of treated lesion at excision as determined by visual assessment (no residual tumor seen on visual inspection) • Histological clearance of treated lesion(s) at excision • Abscopal effect as determined by clinical and histological clearance of nontreated lesions at excision • Estimate of remaining tumor volume (necrotic cells:tumor cells) • PGA
• To characterize the pharmacokinetics (PK) of an 8 mg dose of VP-315 administered with the optimal dosing regimen	• Plasma VP-315 concentrations

Exploratory Objectives	**Endpoints**
• To assess subject and physician satisfaction with the treatment	• SCAR-Q, FACE-Q • Scar Cosmesis Assessment and Rating (SCAR) Scale
• To assess the immune response to VP-315 treatment in a subset of subjects by assessing the immune repertoire in blood and in tissue	• Multiplex immunohistochemical staining for T-cell subsets and immune activation markers in tumor tissue samples • Analysis of T-cell clonality in blood and tumor tissue samples

4. EXPERIMENTAL PLAN

4.1 Study Design

This is a 2-part, open-label, multicenter, proof-of-concept study with a safety run-in designed to assess the safety, tolerability, MTD, and objective antitumor efficacy of VP-315 when administered intratumorally to adults with biopsy-proven BCC.

The study is expected to enroll approximately 80 subjects with a histological diagnosis of BCC in at least 1 eligible target lesion (confirmed by punch or shave biopsy).

All enrolled subjects will receive VP-315 intradermal injection on an outpatient basis into up to 2 target lesions. In all Parts of the study (1, or 2, as below), each 7-day treatment week comprises up to 3 consecutive treatment days followed by a no-treatment period of at least 4 days. Dosing will commence in a single target lesion. In Study Part 1 and Study Part 2 (Cohorts 1-2), once a target lesion has necrosed, treatment of that lesion stops, and treatment of subsequent target lesions (up to 2 total) may continue on Day 1 of the following week (week 2) (see Section 7.3.2).

Part 1 (N= 2 to 8): VP-315 once-daily dosing; starting total daily dose of 2 mg for the first subject. Ascending once-daily 1-mg dosing increments (e.g., 2 mg on Day 1, 3 mg on Day 2). Subjects may be treated for a maximum of 2 weeks and a maximum total daily dose of 8 mg in Part 1. The starting dose will be escalated between subject cohorts in 1-mg increments after the previous cohort has completed Week 1 dosing (the DLT observation period) (Table 7-1).

Part 2 (N= Approximately 66 to 72):VP-315 once-daily dosing; will be a total daily dose of 8 mg in up to 5 cohorts (i.e, there were no DLTs that occurred during Part 1 of the study and the maximum dose of 8 mg was achieved).

- **Cohort 1** (N=3 to 6): VP-315 once-daily dosing of 8 mg with a loading dose of half the target dose of 8 mg (i.e., 4 mg) only on W1D1; the remaining 2 doses in the first treatment week (up to 3 consecutive daily doses) will be the full target dose of 8 mg without a loading dose. Subjects will be treated until the lesion is necrosed, for a maximum of 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3- up to 6 total doses).
- **Cohort 2** (N=3 to 6): VP-315 once-daily dosing of 8 mg on all treatment days (i.e., NO LOADING dose on W1D1) for up to 3 consecutive daily doses/week until the lesion is necrosed, for a maximum of 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3- up to 6 total doses).

The study design and dosing strategy listed below for Cohorts 3, 4 and 5 are recommendations from the Safety Review Committee following an adhoc safety review meeting held on June 13-14, 2023 to discuss subjects reports of pain and burning at the injection site that were not observed in Part 1 of the study:

- Recommendation: Remove/skip Cohort 3 in Part 2 of the protocol and advance from Cohort 2 to Cohorts 4 and 5. Revert to Part 1 dosing strategy of a 30/70 split dose for all treatments with the injections adminstered 15-minutes apart.

Cohort 3: (N=0): This cohort has been removed at the recommendation of the SRC.

For Part 2 (Cohorts 4 and 5) the highest total daily dose of VP-315 (8.0 mg) will be divided into a split dose; the first dose is not to exceed 2.4 mg (30% of 8-mg dose), and the remaining dose will not exceed 5.6 mg (70% of 8-mg dose) and administered 15 minutes apart (not to exceed 30 minutes).

- **Cohort 4** (N= Approximately 30 (10 initial/up to 20 expansion): (Two times weekly dosing) VP-315 once-daily dosing of 8 mg, administered 2 consecutive days in one week (W1D1, W1D2). The planned dosing regimen will be a split dose of VP-315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second target lesion may begin on D1 of the next week (W2D1, W2D2). Each individual target lesion is treated for the assigned 2 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 4 total doses**.
- **Cohort 5** (N= A**pproximately** 30 (10 initial/up to 20 expansion): (Three times weekly dosing) VP-315 once-daily dosing of 8 mg, administered 3 consecutive days in one week (W1D1, W1D2, W1D3). The planned dosing regimen will be a split dose of VP-315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second target lesion may begin on D1 of the next week (W2D1, W2D2, W2D3). Each individual target lesion is treated for the assigned 3 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 6 total doses**.

See (Table 7-1).

The decision to initiate the next higher dose in Part 1 will be made by an SRC (described in Section 7.4) on the basis of a review of all safety data, and laboratory findings.

Subjects will be screened within 42 days prior to receiving the first dose of VP-315 (biopsy may be collected within 90 days of W1D1); procedures are described in Table 8-1. On W1D1, after completion of all predose procedures, study subjects will receive the first dose of VP-315. Thereafter, each subject in Part 1 and Part 2 (Cohorts 1and 2) will be dosed every day until necrosis of the target lesion for up to 3 consecutive days before entering the no-treatment period. Once a target lesion has necrosed, treatment of that lesion stops, and treatment of any subsequent target lesions (up to 2 total) may continue on Day 1 of the following week (see Section 7.3.2).

In Part 1, DLT or visual confirmation of necrosis of all target lesions will result in termination of VP-315 dosing.

In Part 2 (Cohorts 1and 2) will determine the optimal dosing regimen based on efficacy, safety and tolerability. In Cohorts 4 and 5, the optimal dosing regimen (as determined from Cohorts 1 and 2 or Part 1) will be administered in up to 2 target lesions on either 2 or 3 consecutive days, respectively, regardless of whether necrosis occurs.

Subjects in Part 2 (Cohorts 4 and 5) with only 1 target lesion, that complete week one of treatment and the W1 safety assessment visit without complete necrosis, should return for a Limited Safety Assessment Visit on W2D1 for further evaluation of the lesion for necrosis. No additional treatment will be provided.

Subjects in Part 2 (all Cohorts) that complete week two of treatment and the W2 Safety Assessment Visit without complete necrosis, should return for a Limited Safety Assessment visit on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be provided.

For the first 10 subjects enrolled into Part 2 (Cohorts 4 and 5): after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring).

Following the final treatment of the 10th subject in Cohort 4, enrollment into Cohort 5 may be initiated for 10 subjects.

Cohort 4 expansion group:

An SRC meeting was convened after the 10 subjects in Cohort 4 completed the Safety Assessment and approved the following:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 4.
- After each treatment, the additional subjects enrolled into Cohort 4 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

Cohort 5 expansion group:

An SRC meeting was convened after the 10 subjects in Cohort 5 completed the Safety Assessment and approved the following:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohort 5.
- After each treatment, the additional subjects enrolled into Cohort 5 expansion: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

Plasma PK sampling will be collected in subjects in Part 2 (Cohorts 4 and 5 expansion group) as detailed in Table 8-1.

Four to 6 weeks in Part 1, and 12 to 14 weeks (Part 2) after the first injection of VP-315, subjects will return for all target and nontarget BCC lesions (Section 5.4) to be excised for histological evaluation. If the lesion(s) has clinically cleared, the area where the lesion was will be excised, and tissue samples will be sent to the central dermatopathologist for analysis/histology. Suture removal and final photography should occur 7 (±1) or 14 (±2) days after excision (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 end-of-study (EOS) visits accordingly.

During the study period, subjects will be expected to visit the study facility and complete study procedures as outlined in the schedule of assessments (Table 8-1).

If there is a clinically significant AE or abnormal laboratory result at the EOS visit, follow-up (F/U) visits may be required until resolution of the abnormality, or until the condition is considered clinically stable.

4.2 Number of Sites

There will be up to 15 study sites in the US that will participate in this study.

4.3 Estimated Study Duration

4.3.1 Study Duration for Subjects

The treatment duration for each subject is variable—each subject will receive VP-315 for up to a maximum of 2 weeks. In Part 1, in the event of DLT or necrosis of all target lesions, treatment will be stopped.

All lesions will be excised 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after the W1D1 injection. The study duration for each subject is variable as a subject may require F/U visit at 1- or 2- weeks post-excision.

The study will require approximately 17 months from the time that the first subject provides signed informed consent through the last subject's last study-related visit (up to 42 days Screening; treatment in 1-week intervals until visual confirmation of necrosis of target lesions; surgical excision of all target and nontarget lesions 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after W1D1 injection; F/U visit at 1 or 2 weeks post-excision).

4.3.2 End of Study

Surgical excision of all target and nontarget BCC lesions will occur 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after the W1D1 injection, and a F/U visit will take place 1- or 2- weeks post-excision (EOS visit). Suture removal and final photography should occur 7 (±1) or 14 (±2) days after excision (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 EOS visits accordingly. Scar Cosmesis Assessment and Rating (SCAR) Scale will be completed by the site investigator prior to excision at the EOS Visit (Part 2: Cohorts 4 and 5).

5. STUDY POPULATION

Before any study-specific procedure may be performed, the appropriate written informed consent must be obtained (see Section 12.2).

Investigators will be expected to maintain a screening log in the electronic CRF of all potential study candidates who sign the informed consent form (ICF) that includes limited information about the potential candidate (age, gender, race), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate).

5.1 Number of Subjects

Safety Run-in (Part 1 of the Study)

Approximately 2-8 subjects with a histological diagnosis of BCC will be enrolled for treatment with VP-315 in Part 1.

Dosing Regimen Optimization and Confirmation (Part 2 of the Study)

Approximately 66-72 subjects with a histological diagnosis of BCC will be enrolled for treatment with VP-315 in Part 2.

5.2 Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

7. Adults ≥18 years of age
8. Clinically suspected BCC with at least 1 (and up to 5) eligible lesion(s) suitable for biopsy and excision (see Section 5.4)
9. Willing to refrain from using nonapproved topical agents on, or within 2 cm of, the target BCC lesions and surrounding areas during the treatment period. Subjects should use topical agents that are gentle (e.g., Aquaphor®, CeraVe®) and will not irritate the skin in these areas
10. Willing to refrain from exposure to direct sunlight or ultraviolet light and to avoid the use of tanning parlors for the duration of the study
11. Written informed consent obtained, including consent for tissue to be examined by the central dermatopathologist and stored by the Sponsor or designee
12. Willing to undergo BCC surgical excision procedure of target and nontarget BCC lesions after study treatment
13. Willing to delay surgical excision of target and nontarget BCC lesions until the end of treatment (EOT) visit

14. Provides written consent to allow photographs of the target and nontarget BCC lesion to be used as part of the study data
15. Willing to practice a highly effective method of birth control while on study and until 4 weeks after the last treatment. Highly effective birth control includes sexual abstinence, vasectomy, bilateral tubal ligation/occlusion, or a condom with spermicide (men) combined with hormonal birth control or intrauterine device in women.

5.3 Subject Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study.

1. Presence of known or suspected systemic cancer
2. Treatment with systemic chemotherapeutic agents within the 6 months prior to the screening visit
3. Treatment with systemic immunotherapy, immunomodulators or immunosuppressants within the 12 weeks prior to the screening period
4. Genetic or nevoid conditions (e.g., Gorlin / basal cell nevus syndrome, xeroderma pigmentosum
5. Clinically significant laboratory values, as assessed by the investigator, for the tests listed in the Schedule of Assessments, including:
    a. serum creatinine >1.5× the upper limits of normal and
    b. serum tryptase concentration >11.4 ng/mL
6. Chronic medical condition such as, but not limited to:
    a. Uncontrolled infection or infection requiring antibiotics
    b. Uncontrolled cardiac failure: Classification III or IV New York Heart Association
    c. ***Subjects presenting with a systolic BP <110 mmHg and/or diastolic BP <70 mmHg at Screening or Week 1 Day 1 or a*** history of cerebrovascular or cardiac disorders, or subjects at particular risk of sequelae following a short hypotensive episode.
    d. Uncontrolled systemic or gastrointestinal inflammatory conditions
    e. Known bone marrow dysplasia
    f. History of positive tests for human immunodeficiency virus/acquired immunodeficiency syndrome or active hepatitis B or C
    g. History of systemic autoimmune disease requiring anti-inflammatory or immunosuppressive therapy within 3 months prior to Day 1, with the following exceptions:
        i. Subjects with a history of autoimmune thyroiditis are eligible provided the subject requires only thyroid hormone replacement therapy and disease has been stable for ≥1 year

ii. Subjects with well-controlled type I diabetes (in the opinion of the investigator) are eligible

h. Known mast cell activation syndrome, mastocytosis, or chronic idiopathic urticaria

7. Known sensitivity to any of the ingredients in the study medication
8. Elective surgery within 4 weeks prior to the screening visit, during the study, or 4 weeks after the treatment period
9. Evidence of current chronic alcohol or drug abuse
10. Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of the screening visit
11. In the investigator's opinion, evidence of unwillingness, or inability to follow the restrictions of the protocol and complete the study
12. Females who are pregnant or breastfeeding.

5.4 BCC Lesion Eligibility

Eligible lesions are those that meet the BCC lesion eligibility specifications described herein, from samples that are either from:

- *HISTORICAL* punch or shave biopsies (i.e., samples collected according to clinical standard of care collected within the 90 days prior to W1D1);
- A 2-mm punch biopsy collected within 90 days of W1D1 for suspected BCC ≥0.5 cm to 1.0 cm, and 3-mm punch biopsy for suspected BCC >1.0 cm to 2.0 cm; or
- A shave biopsy performed according to standard of care to include superficial or middle papillary dermis collected within 90 days of W1D1.

Lesions must meet the following criteria to be eligible for treatment with VP-315 as target lesions or for observation as nontarget lesions. Up to 2 target lesions may be treated, and any eligible lesions that do not receive treatment (up to 3) will be tracked as nontarget lesions for abscopal effect.

Lesions that meet the inclusion criteria and are only excluded by Criteria 6 through 9 in Section 5.4.2 below (TARGET LESION EXCLUSION) may be tracked as nontarget lesions. Lesions that do not meet the inclusion criteria or are excluded by BCC Lesion Exclusion Criteria 1 through 5 below will not be treated or observed (i.e., ineligible) and should be excised after completion of the study unless otherwise clinically indicated.

5.4.1 BCC Lesion Inclusion Criterion

1. For punch biopsies: the size of the lesion(s) must be ≥0.5 cm and ≤2 cm in the longest diameter prior to punch biopsy.

2. Histological diagnosis of nodular, micronodular, or superficial BCC, as confirmed by punch or shave biopsy performed within 90 days of W1D1. (NOTE: *HISTORICAL* punch or shave biopsies are acceptable, provided that the biopsy was performed according to clinical standard of care and was collected within the 90 days prior to Screening W1D1.)

5.4.2 BCC Lesion Exclusion Criteria

1. Recurrent or previously treated lesions
2. Lesions within 1 cm of the eyelids or lips, or on the hands, feet, ears, nose, and genitalia
3. Histological evidence of any other tumor in the biopsy specimen
4. Histological evidence of infiltrative, desmoplastic, sclerosing, or morpheaform BCC subtypes in the biopsy specimen
5. Medium- and high-risk basal cell carcinomas as defined by the National Comprehensive Cancer Network (NCCN) or Mohs Appropriate Use Criteria (i.e., BCCs eligible for Mohs surgery).

TARGET LESION EXCLUSION ONLY:

6. For subjects with severe stasis dermatitis, target BCC lesions may not be on the lower extremities
7. Within 2 cm of the target BCC lesion(s):
    a. Treatment with the following topical agents within the 12 weeks prior to the screening visit: aminolevulinic acid, 5-fluorouracil, corticosteroids, diclofenac, imiquimod, ingenol mebutate
    b. Treatment with surgical excision, or curettage within the 2 weeks prior to the screening visit
    c. Evidence of dermatological disease or confounding skin condition that may interfere with clinical evaluation (i.e., psoriasis, atopic dermatitis, eczema, propensity to form keloids or hypertrophic scarring)
    d. Use of topical immunomodulators during study
8. Within 5 cm of the target BCC lesion(s): history of any skin cancer, except for other currently identified target and nontarget BCC lesions
9. Target BCC lesion is in the area of prior resurfacing procedure with CO_2 laser or any photodynamic and phototherapy treatment within the 3 months prior to the screening visit.

6. SUBJECT ENROLLMENT

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study.

Approximately 80 adult subjects ≥18 years of age will be enrolled into the study.

Before subjects begin participation in any study-specific activities/procedures, the Sponsor requires a copy of the site's written Institutional Review Board (IRB) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable. All subjects and/or legally acceptable representatives must personally sign and date the ICF before commencement of study-specific activities/procedures.

When the investigator determines that the subject meets all of the inclusion criteria (Section 5.2) and none of the exclusion criteria (Section 5.3), confirmation of eligibility and the date of confirmation is recorded in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject provides written informed consent) receives a unique identification number before any study procedures are performed.

Subjects who meet the eligibility requirements for entry into this open-label study (Section 5.2 and Section 5.3) will be sequentially enrolled, with each subject receiving the next available subject number (beginning with 001). Enrolled subjects will receive study drug on Day 1 in accordance with the study treatments described in Section 4.1 (Figure 7-2).

7. TREATMENT AND TREATMENT PROCEDURES

7.1 Randomization and Blinding

This is an open-label, multicenter, dose-escalating study. Eligible subjects will be enrolled sequentially.

VP-315 will be dispensed by the study pharmacist, or designee, in an open-label fashion to the subjects. All Screening tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. Replacement subjects may be enrolled if subjects do not complete all EOT lesion excisions. Replacement subjects will not be enrolled for subjects who discontinue the study due to treatment-related toxicity, including subjects who have not completed all lesion excisions. A new unique subject number will be assigned to the replacement subject.

7.2 Description and Handling

7.2.1 Formulation

LTX-315 is an oncolytic peptide provided as LTX-315 Acetate 20 mg/vial lyophilized powder for injection that will be reconstituted in saline to a concentration ranging from 4 to 20 mg/mL based upon the target dose and volume for each subject. The single excipient, water for injection (WFI), is of pharmacopeial quality; the WFI is removed by lyophilization. LTX-315 is supplied in colorless glass vials (Ph. Eur. hydrolytic class I) fitted with a rubber stopper (Ph. Eur. type I).

7.2.2 Storage and Handling

Unreconstituted LTX-315 vials (20 mg/vial) must be stored as follows:

- refrigerated at 2-8°C (36- 46°F) ***or***
- frozen at -20 ± 5 °C (-13° to 5°F)
- protected from light at the study site, separated from other drugs.

The reconstituted LTX-315 solution can be stored for up to 12 hours in a refrigerator at 2-8°C (36–46°F). Syringes with LTX-315 drawn from the vial can be stored for up to 4 hours at 20-25°C (68-77°F) protected from light. Any unused portion should be discarded.

Storage conditions for LTX-315 are specified on the label. All vials of investigational product should be stored in a securely locked area, accessible only to authorized site personnel until reconstitution. To ensure the stability and proper identification, investigational product should not be stored in a container other than the containers in which they were supplied.

Additional information regarding storage, handling and reconstitution is provided in the Pharmacy Manual.

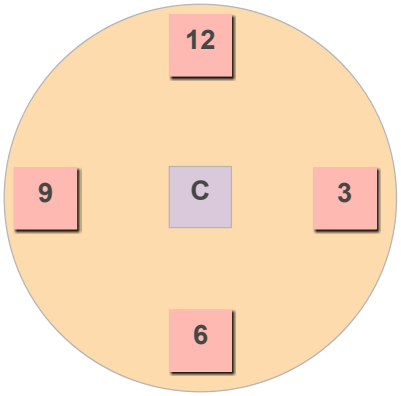
7.3 Dosage, Administration, and Schedule

VP-315 will be administered via intradermal injection into a single target lesion (between ≥0.5 cm and ≤2 cm in longest diameter) using the 1-mL syringe and 30-gauge ½-inch needle provided by Verrica. The subjects should be positioned in a way so that the target lesion lies flat, to avoid any dependent areas that may be susceptible to leakage of VP-315. Subsequent injections for the same lesion will be given in remaining nonnecrotic areas of the lesion, as assessed prior to treatment. In Parts 1 and Part 2 (Cohorts 4 and 5), each 500-µL dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. In all parts of the study, the targeted total volume of delivery is 500 µL daily.

In Part 2, refer to Table 7-1 for cohort dosing and regimen.

For all injections, VP-315 is injected intradermally. It is critical to assure adequate and even distribution of VP-315 across the entire base of the lesion. To accomplish this, the first 150 µL is to be injected as centrally as possible such that the VP-315 can distribute radially outward. The second (350-µL) portion shall be injected in a clockface fashion (i.e., 12, 3, 6, 9 o'clock [*shown below in Figure 7-1*]) as needed to ensure uniform distribution, into the edges of the lesion to infiltrate the entire tumor with VP-315. Insert the needle at a 10- to 20-degree angle for a flat lesion, or at an increased angle for a raised lesion. Subcutaneous injection should be avoided.

Figure 7-1
Injection Pattern for VP-315



The maximum total daily dose of VP-315 in any treatment visit in any subject or cohort must not exceed 8 mg.

7.3.1 Management of Postinjection Reactions to VP-315

Should a subject experience a post-injection reaction to VP-315 administration, the investigator should treat the subject in accordance with institutional guidelines.

In Part 1, for any Grade 1 (per CTCAE V5) postinjection reaction (with the exception of local reactogenicity) occurring during VP-315 injections, or within 1 hour after the last injection, injections should stop until resolution of the reaction. If the reaction occurs during the first injection of the dose and resolves within 1 hour, the second injection of the dose may continue.

For Grade 2 and higher reactions, the investigator must stop further injections in accordance with TRAE SI/DLT descriptions (Section 10.2).

In Part 2, subjects will continue to be closely monitored for any safety signaling. If a TRAE SI is identified (Section 10.2), the medical monitor will review and determine if treatment should be continued.

7.3.2 VP-315 Dosing Strategy

7.3.2.1 Study Part 1

In Part 1 of the study, the starting total daily dose for the evaluation of VP-315 will be 2 mg for the first subject. Subjects will receive ascending once-daily doses (increasing in 1-mg increments for up to 3 days in a 7-day treatment week [≥4 days off between treatment weeks]) until the first lesion is necrosed or until the subject experiences a DLT, whichever occurs first (Figure 7-2). Subjects will be observed for DLTs throughout the treatment period during Part 1.

After receiving a dose, the subject will return to the clinic the following day for assessment by the investigator. If, in the opinion of the SRC (see Section 7.4), there has been no DLT and if the lesion is not necrotic, the dose will be escalated, and the same lesion will continue to be treated before any additional target BCC lesions may be treated.

When a target lesion is deemed necrotic in the opinion of the SRC, the subject will not receive any additional treatment for that lesion, and a safety assessment visit will be performed instead. If the subject has additional lesions and no DLT has occurred, treatment of the next lesion may begin on day 1 (D1) of the next week. A maximum of 2 target BCC lesions may be treated, and only 1 lesion may be treated at a time. Subjects will be treated for a maximum of 2 weeks and a maximum total daily dose of 8 mg.

The starting dose will be escalated between subject cohorts in 1-mg increments after the previous cohort has completed Week 1 dosing (the DLT observation period) (Table 7-1). Dose escalation in Part 1 will end when 2 subjects experience a DLT at the same nominal dose (indicating that the preliminary MTD has been exceeded, and the preliminary MTD is the dose immediately below where any DLT occurred) or until a maximum VP-315 total daily dose of 8 mg is reached in up to 6 subjects.

7.3.2.2 Study Part 2

Part 2 will be initiated upon completion of Part 1 to determine the optimal dosing regimen of VP-315. There were no DLTs observed in Part 1 of the study and the maximum dose of 8 mg was achieved. Therefore, the dose to be evaluated in Part 2 will be a total daily dose of 8 mg in the following 5 Cohorts:

- **Cohort 1** (N=3-6): The planned dosing regimen in Week 1 of Part 2 will begin with a VP-315 loading dose on Week 1/Day 1 (W1D1) at half the target dose, followed by total daily doses at the full target dose for the remaining dosing days of the treatment week, until the lesion is necrosed. Additional weeks of treatment will not include a loading dose on W2D1. Subjects may be treated for a maximum of 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3 – **up to 6 total doses**).

- **Cohort 2** (N=3-6): VP-315 once-daily dosing of 8 mg on all treatment days (i.e., no loading dose on W1D1) up to 3 consecutive daily doses/week for up to 2 weeks (W1D1, W1D2, W1D3 and W2D1, W2D2, W2D3 – **up to 6 total doses**).

The study design and dosing strategy listed below for Cohorts 3, 4 and 5 are recommendations from the Safety Review Committee following an adhoc safety review meeting held on June 13-14, 2023 to discuss subjects reports of pain and burning at the injection site that were not observed in Part 1 of the study:

- Recommendation: Remove/skip Cohort 3 in Part 2 of the protocol and advance from Cohort 2 to Cohorts 4 and 5. Revert to Part 1 dosing strategy of a 30/70 split dose for all treatments with the injections adminstered 15-minutes apart.

Cohort 3 (N=0): This cohort has been removed at the recommendation of the SRC.

For Part 2 (Cohorts 4 and 5) the highest total daily dose of VP-315 (8.0 mg) will be divided into a split dose; the first dose is not to exceed 2.4 mg (30% of 8-mg dose), and the remaining dose will not exceed 5.6 mg (70% of 8-mg dose) and administered 15 minutes apart (not to exceed 30 minutes).

- **Cohort 4** (N= Appproximately 30 (10 initial/up to 20 expansion): (Two times weekly dosing) VP-315 once-daily dosing of 8 mg, administered 2 consecutive days in one week (W1D1, W1D2). The planned dosing regimen will be a split dose of VP-315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second target lesion may begin on D1 of the next week (W2D1, W2D2). Each individual target lesion is treated for the assigned 2 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 4 total doses.**

- **Cohort 5** (N= Approximately 30 (10 initial/up to 20 expansion): (Three times weekly dosing) VP-315 once-daily dosing of 8 mg, administered 3 consecutive days in one week (W1D1, W1D2, W1D3. The planned dosing regimen will be a split dose of VP-

315 for all treatments. The 500µL (8 mg) dose will be divided into 2 injections given at least 15 minutes and no more than 30 minutes apart, with 30% (150 µL) administered in the first injection and the remaining 70% (350 µL) with the second injection. Treatment for a second target lesion may begin on D1 of the next week (W2D1, W2D2). Each individual target lesion is treated for the assigned 3 days only (regardless of necrosis status). Up to 2 target lesions may be treated – **up to 6 total doses.**

After receiving a dose, the subject will return to the clinic the following day for assessment by the investigator. If, in the opinion of the Medical Monitor, the lesion is not necrotic Cohorts 1 and 2 only, the same lesion will continue to be treated before any additional target BCC lesions are treated. When a lesion is deemed necrotic in the opinion of the Medical Monitor, the subject will not receive any additional treatment for that lesion.

- If the subject has additional lesions, treatment of the next lesion may begin on D1 of the next week. A maximum of 2 target BCC lesions may be treated, and only 1 lesion may be treated at a time.
- Subjects in Cohorts 4 and 5 with only 1 target lesion that complete week one of treatment and the W1 safety assessment visit without complete necrosis should return for a Limited Safety Assessment Visit on W2D1 for further evaluation of the lesion for necrosis. No additional treatment will be provided.
- Subjects in Part 2 (all Cohorts) that complete week two of treatment and the W2 Safety Assessment Visit without complete necrosis should return for a Limited Safety Assessment visit on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be provided.

For the first 10 subjects enrolled into Cohorts 4 and 5: after each treatment, subjects will remain in the study center for up to 2 hours post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring).

Following the final treatment of the 10th subject in Cohort 4, enrollment into Cohort 5 may be initiated for 10 subjects.

SRC Meetings

Two separate SRC meetings were convened after 10 subjects in each initial cohort (4 and 5) completed the Safety Assessment Visit to review the following topics:

- to review the safety signals that may have occurred that could impact further treatment
- to determine if the 2-hours of safety monitoring could be reduced to 1-hour post 2nd injection at treatment (an additional hour may be continued at the discretion of the PI).
- to dermine if enrollment could be expanded to include up to 20 additional subjects for a total of approximately 30 subjects in each cohort.

The SRC approved the following for both Cohorts 4 and 5:

- Up to 20 additional subjects (for a total of approximately 30 subjects) will be enrolled into Cohorts 4 and 5 (expansion groups) respectively.

- After each treatment, the additional subjects enrolled into Cohorts 4 and 5 expansion groups: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI.

Plasma PK sampling will be collected in subjects in Cohorts 4 and 5 expansion group as detailed in Table 8-1.

Twelve to 14 weeks after the first injection of VP-315, subjects will return for all target and nontarget BCC lesions (Section 5.4) to be excised for histological evaluation. If the lesion(s) has clinically cleared, the area where the lesion was will be excised, and tissue samples will be sent to the central dermatopathologist for analysis/histology. Suture removal and final photography should occur 7 (±1) or 14 (±2) days after excision (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 end-of-study (EOS) visits accordingly.

During the study period, subjects will be expected to visit the study facility and complete study procedures as outlined in the schedule of assessments (Table 8-1).

Management of TRAEs/TRAE SIs (see Sections 7.3.1and 10.2)

Subject dosing will continue until any TRAE of any grade occurs, with the exception of Grade 1 TRAEs indicative of local reactogenicity (injection-site pain, erythema, induration). Systemic reactogenic AEs (fever, myalgia, headache) and Grade 2 local reactogenic AEs will be considered TRAEs of special interest (Section 10.2).

If a TRAE SI is identified, the site will notify the medical monitor who will review and determine if treatment should be continued.

For TRAE SIs occurring during VP-315 injections, or within 1-hour after the last injection, injections should stop until resolution of the reaction. If the reaction occurs during the first injection of the dose and resolves within 1-hour, the second injection of the dose may continue.

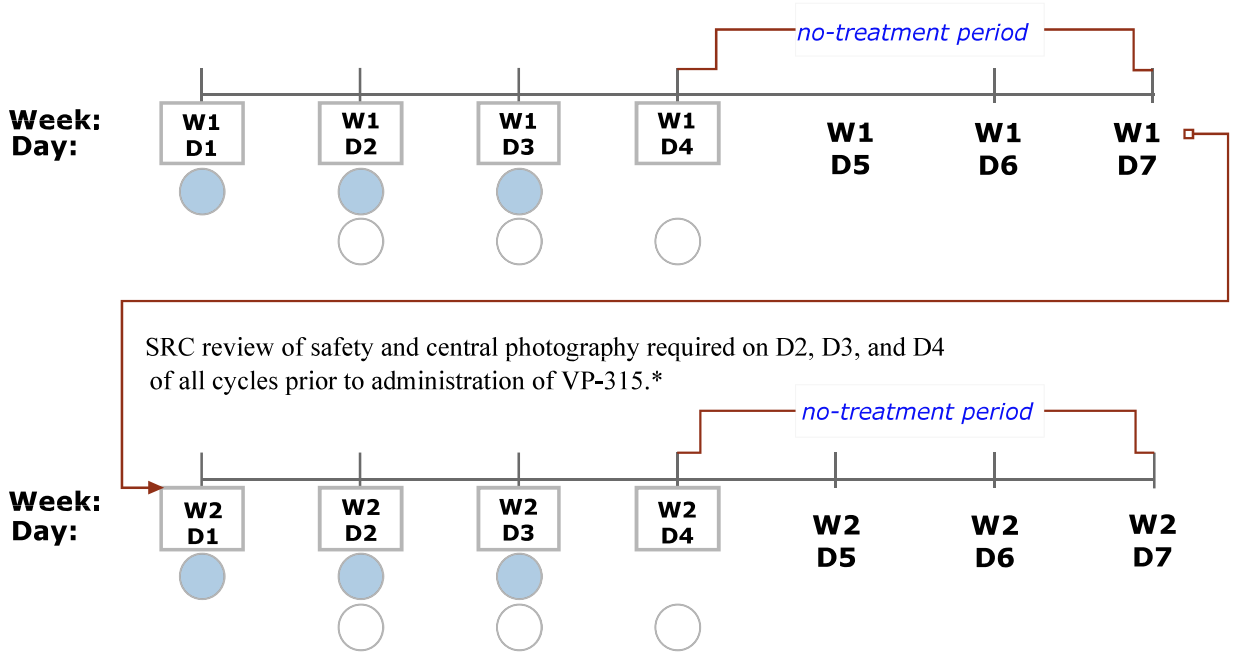
For TRAE SIs Grade 2 (per CTCAE V5) and higher reactions, the investigator must stop further injections in accordance with TRAE SI/DLT descriptions (Section **10.2**) and Tryptase must be collected per protocol (Section 8.4.5).

If there is a clinically significant AE or abnormal laboratory result at the EOS visit, follow-up (F/U) visits may be required until resolution of the abnormality, or until the condition is considered clinically stable.

All AEs including TRAE SIs should be recorded on the subject's AE Form.

Subjects may be discontinued for AEs at any time per the discretion of the investigator.

Figure 7-2
Dosing Schema, Intra-subject Escalation (Part 1)



= **VP-315 Treatment.** Dose increases by 1 mg each treatment day unless there is DLT or significant necrosis.

= Safety assessment. D2 through D4 visits could be treatment (following SRC review), OR Safety assessment only, if DLT or significant necrosis is present.

= Boxed Study Week/Day indicates visits in the study center.

***NOTE**: Treatment continues until DLT or significant necrosis of Target Lesion #1 as determined by SRC. If significant necrosis is determined, the current assessment is changed to an assessment-only visit, and no VP-315 is administered for remaining days of the current Treatment Interval/Week. If the subject has an additional an additional target lesion and DLT has not occurred, treatment of Target Lesion #2 may begin at D1 of next Treatment Interval/Week. Up to 2 target lesions may be treated.

The maximum total daily dose of VP-315 in any treatment visit in any subject or cohort must not exceed 8 mg.

Table 7-1 Dose Regimen (Part 2 Cohorts 1-5)

CRO must be contacted for each subject before treatment to confirm Cohort assignment

Cohorts	**W1D1**	**W1D2**	**W1D3**	**W1D4**	**W2D1**	**W2D2**	**W2D3**	**W2D4***
Cohort 1 – loading dose (N=3 to 6)	**4 mg loading**	**8 mg**	**8 mg**	**Safety**	**8 mg**	**8 mg**	**8 mg**	**Safety**
	• *If no TRAE SI in the first 3 subjects, then begin enrollment into* ***Cohort 2***							
	• *If 1 TRAE SI occurs in the first 3 subjects, enroll up to 6 subjects*							
	– *If no further TRAEs SI occur, then begin enrollment into* ***Cohort 2***							
	– *If 2 TRAEs SI occur in 6 subjects, then begin enrollment into* ***Cohort 3***							
Cohort 2 – No loading dose (N=3 to 6)	**W1D1**	**W1D2**	**W1D3**	**W1D4**	**W2D1**	**W2D2**	**W2D3**	**W2D4**
	8 mg	**8 mg**	**8 mg**	**Safety**	**8 mg**	**8 mg**	**8 mg**	**Safety**
	• *If no TRAE SI in the first 3 subjects, then begin enrollment into* ***Cohort 4***							
	• *If 1 TRAE SI occurs in the first 3 subjects, begin enrollment into Cohort 4 with 30/70 split dosing of 8mg for each treatment*							
Cohort 3 – has been removed								

NOTE: Cohorts 1-2: Treatment continues until TRAE (includes TRAE SI) or significant necrosis of Target Lesion #1 as determined by Sub-SRC. If significant necrosis is determined, the current assessment is changed to an assessment-only visit, and no VP-315 is administered for the remaining days of the current Treatment Interval/Week. If the subject has an additional target lesion and a TRAE has not occurred, treatment of Target Lesion #2 may begin at D1W2 of next Treatment Interval/Week. Up to 2 target lesions may be treated. Subjects that complete two weeks of treatment and the W2D4 Safety Assessment Visit without achieving complete necrosis, should return for a Limited Safety Assessment Visit on W3D1 for further evaluation of the lesion for necrosis.

Cohort 4 **2-day dosing regimen** **N=30** **(10 initial/ 20 expansion)**	**Lesion #1 Treatment**				**Lesion #2 Treatment**				
	W1D1	**W1D2**	**W1D3**	**W2D1**	**W2D1**	**W2D2**	**W2D3**	**W3D1**	
	30/70 8 mg	**30/70 8 mg**	**Safety**	**Limited Safety**	**30/70 8 mg**	**30/70 8 mg**	**Safety**	**Limited Safety**	
Cohort 5 **3-day dosing regimen** **N=30** **(10 initial/ 20 expansion)**	**Lesion #1 Treatment**					**Lesion #2 Treatment**				
	W1D1	**W1D2**	**W1D3**	**W1D4**	**W2D1**	**W2D1**	**W2D2**	**W2D3**	**W2D4**	**W3D1**
	30/70 8 mg	**30/70 8 mg**	**30/70 8 mg**	**Safety**	**Limited Safety**	**30/70 8 mg**	**30/70 8 mg**	**30/70 8 mg**	**Safety**	**Limited Safety**

NOTE: Cohorts 4-5: The administration strategy will be based on the recommendation of the SRC, utilizing Part 1 dosing administration of 30/70 split for 2 or 3 consecutive days. Target Lesion #2 may begin at D1 of next Treatment Interval/Week. Each individual target lesion is treated per cohort regimen of 2- or 3-days only (not based on necrosis). Up to 2 target lesions may be treated. Subjects with only 1 target lesion, that complete week one of treatment and the W1 safety assessment visit without complete necrosis should return for a Limited Safety Assessment Visit on W2D1 for further evaluation of the lesion for necrosis. Subjects with 2 target lesions, that complete two weeks of treatment and the W2 Safety Assessment Visit without achieving complete necrosis, should return for a Limited Safety Assessment Visit on W3D1 for further evaluation of the lesion for necrosis.

7.4 Dose Escalation and Stopping Rules

7.4.1 Safety Review Committee

An SRC, comprising at least 2 Sponsor representatives (including the appointed Medical Monitor) and at least 1 investigator, will convene between study Parts to review data, monitor safety, and if warranted, suggest changes to the VP-315 dose.

In addition, there will be a sub-SRC that is responsible for continued oversight and monitoring with a Sponsor-appointed Medical Monitor or designee and an Independent Reviewer to assist with real-time virtual review and assessment beginning on W1D2; this review will assist in determining the need for additional intra-subject treatments, necrosis, dosing instruction, AE reporting, and stopping rules.

Safety data from the current subject or cohort and previous cohorts will be reviewed by the sub-SRC prior to the sub-SRC authorizing dose escalation (Part 1 only) for the next dose level. The decision to halt or proceed with the planned dose escalation schedule, or modify the schedule as appropriate, will be made by the sub-SRC after careful consideration of all available safety and central photography information. The SRC will recommend phase 2 dose/regimen for the study.

Any detected toxicity may require dose reductions, dose-schedule changes, or other action(s) as appropriate, including further refinement of the MTD. If a safety stopping rule criterion is observed (e.g., occurrence of a DLT), an ad hoc meeting of the SRC will convene to assess the AEs or findings. Safety findings will be reported to the investigators, the IRB, and any other appropriate regulatory authorities.

After determination of the cause and significance of safety events, the SRC is empowered to recommend continuing enrollment of the current cohort, pausing of enrollment, ceasing dose escalation, changing the protocol and study assessments to enhance subject safety, or terminating the study, as appropriate. If the investigation indicates a high probability that the observed safety event was due to an identifiable cause other than the study drug, the SRC may recommend continuation of study enrollment.

7.4.2 Dose Escalation

Subjects may be treated for a maximum of 2 weeks and a maximum total daily dose of 8 mg in all parts of the study (1 and 2).

Details of dose escalation are provided in Section 7.3.2. Determination of whether or not to advance VP-315 doses will be made following safety review by the SRC and Sponsor-appointed Medical Monitor (or designee). The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade safety events. The safety review will include at a minimum:

- All AEs, including intensity and investigator assessment of drug causality
- Routine laboratory test results (chemistry, hematology) and available serum tryptase findings

- Treatment-emergent changes on electrocardiogram (ECG)
- Treatment-emergent changes on vital signs

7.4.3 Stopping Rules

In Part 1, any detected toxicity may require dose reductions, dose-schedule changes, or other action(s) as appropriate, including further refinement of the MTD. If a safety stopping rule criterion is observed in Part 2 (e.g., occurrence of a TRAE SI), an ad hoc meeting of the SRC will convene to assess the AEs or findings.

All subjects will be monitored for evidence of DLTs (as defined in Section 10.2). The onset of DLTs will result in termination of dosing in that subject. Additionally, the following considerations will be made based on the occurrence of DLTs:

Part 1 of the study: Dose escalation in Part 1 will end when 2 subjects experience a DLT at the same nominal dose (indicating that the preliminary MTD has been exceeded)

Part 2 of the study: For Grade 2 TRAE SIs and higher (per CTCAE V5), the investigator should discontinue VP-315 treatment, collect Tryptase per protocol (Section 8.4.5) in that subject and the subject should return for all follow-up visits.

In all cases, the SRC will have the authority to discontinue or modify VP-315 dosing if TRAEs, changes in vital signs, ECGs, or clinical laboratory results are observed and these changes are determined to pose a significant health risk to the subject.

7.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.6.1.

All concomitant medications administered while the subject is enrolled in the study (including over-the-counter products) must be recorded on the eCRF, listing generic name or trade name, indication, quantity administered, and date(s) of administration.

Hormonal birth control pills or hormonal replacements may be taken during the course of this study. If necessary, acetaminophen may be administered at the investigator's discretion in single doses of up to 2 g/day. Prophylactic antibiotics may be prescribed and/or administered by the investigator in advance of excision of any target and nontarget lesions.

For itching of the treated areas, subjects are permitted to use gentle topical agents (e.g., Aquaphor®, CeraVe®) that will not irritate the skin in these areas.

7.6 Treatment Restrictions

7.6.1 Prohibited Medications

All prescription medications (other than those specifically excluded in Section 5.3 (*Exclusion Criteria*) that subjects have been prescribed will be continued during the subject's participation in the study.

Subjects should be advised to avoid the use of excluded medications and treatments. If, in the opinion of the investigator, a subject requires any of these medications, the Medical Monitor should be consulted.

Nonapproved topical agents should not be used on, or within 2 cm of, the target BCC lesions and surrounding areas during the treatment period and through the EOS visit.

7.6.2 Other Restrictions

Subjects should be advised to avoid exposure to direct sunlight or ultraviolet light and to avoid the use of tanning parlors for the duration of the study.

During the study, from the time of screening through discharge from the study, subjects are restricted from the following:

- Participating in another clinical trial
- Use of illicit drugs

In addition, subjects should avoid the following unless the investigator feels it is required for subject care or for the treatment of any AEs:

- Receipt of any injections unless the subject has been maintained on the drug prior to being screened for this study

7.6.3 Dietary Restrictions

There will be no dietary restrictions during this study, except under the direction of the investigator.

7.7 For Women of Childbearing Potential

Female subjects of childbearing potential must agree to avoid all means of becoming pregnant for the duration of the study. Subjects may not take part in this study if they are pregnant or are planning to become pregnant during the time they are participating in the study.

Female study subjects of childbearing potential must agree to use a method of birth control that is acceptable to them, their study doctor, and Sponsor for the duration of the study. Women who are postmenopausal for at least 2 years (by history and by confirmed follicle stimulating hormone testing [using local reference ranges]), women with documented total hysterectomy, documented bilateral oophorectomy, and women with documented bilateral tubal ligation are considered to be of nonchildbearing potential.

Pregnancy tests will be given at regular intervals throughout the study for female study subjects of childbearing potential (see Section 10.1.3.3 for additional information).

8. STUDY PROCEDURES

8.1 Screening Assessments

Each subject must sign and date the ICF prior to their participation in any screening activities. Prospective subjects are expected to complete Screening evaluations (exclusive of biopsy) no more than 42 days prior to the planned date of the first study drug administration (Day 1). Note: Subjects with a systolic BP <110 mmHg and/or diastolic BP <70 mmHg at the Screening visit do not meet inclusion criteria and should not be enrolled into the study.

At Screening, subjects will either provide a *HISTORICAL* biopsy (punch or shave) collected according to clinical standard of care within 90 days of W1D1 or will undergo a punch or shave biopsy of the suspected BCC lesions within the 90 days prior to W1D1. All specimens will be sent as slides to the central dermatopathologist for confirmation of eligibility.

Shave biopsies for suspected BCCs will be performed according to standard of care and include superficial or middle papillary dermis; suspected BCC lesions must meet the criteria described in Section 5.4.

Punch biopsies will be collected for suspected BCCs (a 2-mm punch biopsy for suspected BCC ≥0.5 cm to 1.0 cm, and a 3-mm punch biopsy for suspected BCC >1.0 cm to ≤2.0 cm). Biopsy sites should be closed with 1 to 2 non-absorbable sutures (sized 4-0 or 5-0) depending on investigator preference. Up to 5 suspected BCC lesions may be evaluated by punch biopsy during screening. The subject should return during the screening period to have sutures removed in accordance with standard of care.

All on-study treatment day visits and dosing should be scheduled from Day 1 (date of the first dose of study drug).

During the study, every effort should be made to keep subjects on the timetable for procedures and assessments in accordance with the schedule of assessments (Table 8-1).

8.2 Treatment Period

After completion of screening/baseline assessments (Table 8-1), subjects will be enrolled to receive intratumoral VP-315. In Part 1, each 7-day treatment week comprises up to 3 consecutive treatment days followed by a no-treatment period of at least 4 days. Once a target lesion has necrosed, treatment of that lesion stops, and treatment of subsequent target lesions may continue on Day 1 of the following week. Subjects may be treated for a maximum of 2 treatment weeks. In Part 2 of the study, each 7-day treatment week comprises up to 2 or 3 consecutive treatment days followed by a no-treatment period of at least 4 days.

After each treatment, all subjects in Part 1, Part 2 – Cohort 1, Cohort 2 and Cohorts 4 and 5 (first 10 subjects in each) will remain in the study center for up to 2 hours for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring) After each treatment, the additional 20 subjects enrolled into Cohort 4 and 5 expansion groups: will remain in the study center for up to 1-hour (reduced from 2-hours) post second injection for safety monitoring (e.g., continuous blood pressure, electrocardiographic and AE monitoring), an additional hour may be continued at the discretion of the PI. Plasma PK sampling will be collected (in Part 2, Cohorts 4 and 5 expansion groups) as detailed in Table 8-1.

The subject will return to the clinic the day after treatment for assessment by the investigator. The treatment site will be photographed and assessed for CRA (Appendix 1) and PGA of response to treatment (Appendix 2), with images uploaded for real-time assessment by the SRC (Part 1) and/or Medical Monitor (Part 2). The CRA and PGA will be performed by the investigator or trained personnel at each treatment visit, at the EOT visit, and at the EOS visit.

Subjects in Part 2 (Cohorts 4 and5) with only 1 target lesion, that complete week one of treatment and the W1 safety assessment visit without complete necrosis should return for a Limited Safety Assessment Visit on W2D1 for further evaluation of the lesion for necrosis.

Subjects that complete two weeks of treatment and the W2 safety assessment visit without complete necrosis should return for a Limited Safety Assessment Visit on W3D1.

Nontarget BCC lesions will be observed for abscopal effect.

In Part 2 of the study, subject-reported outcomes will be collected with the SCAR-Q (Scar appearance, Scar symptoms, and Psychosocial impact scales) (Appendix 3) and relevant subscales of the FACE-Q (Satisfaction with outcome) completed at each Safety Assessment Visit, and EOT visit.

8.3 End of Study and Follow-up

Subjects will be required to return for excision at the EOT visit and F/U visits regardless of clinical appearance of the lesions, including all subjects who prematurely discontinue administration of the study drug for any reason.

Scar Cosmesis Assessment and Rating (SCAR) Scale will be completed by the PI at the EOT visit, prior to the excision.

In accordance with the procedures noted in Table 8-1, all target and nontarget BCC lesions will be surgically excised with a 3 mm- margin to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after receipt of the W1D1 injection, and a tissue sample will be sent to the central dermatopathologist for analysis/histology. If a lesion has clinically cleared, the area where the lesion was will be excised accordingly.

Suture removal and final photography should occur 7 (±1) or 14 (±2) days after excision (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 EOS visits accordingly.

Subjects will be contacted 30 (± 2) days after last injection with VP-315 to confirm any AEs that have occurred since the last study visit. Subjects attending EOS 30 days post last injection will not require a F/U phone call.

Table 8-1
Schedule of Assessments

Procedure	Screen [a]	Treatment	Treatment Assessment			Follow-up			
		(2 weeks max, each subject)	Safety Assessment Visit	Limited Safety Assessment Visit	EOT (excision)	*Unsched. Visits*	EOS [q]		Follow-up call
							Face	*Body*	
	Day -42 to -1	Day 1-3 of each Week (while lesion is not necrosed)	Day 4 of each Week (or 1 day after last lesion injection upon necrosis)	W2D1 or W3D1 (Part 2) [t]	Day 84-98 (or 12-14 wks from W1D1)		1 Week (7d±2) post excision [q]	2 Weeks (14d ±2) post excision [q]	30 Days post EOS with ongoing Aes [s]
Written informed consent	X								
Eligibility criteria [b]	X								
Vital signs [c]	X	X	X	X	X	X	X	X	
Fitzpatrick Skin Type and lesion count [d]	X								
Medical, surgical and cancer history	X								
Limited physical examination (Dermatologic exam) [e]	X	X	X	X	X	X			
Body weight, height, BMI	X				X				
Electrocardiogram (12-lead) [f]	X	X	X		X				
Cardiac Holter/telemetry (5-lead) [f]		X							
Clinical laboratory assessments [g]	X		X			X	X	X	
Serum tryptase assessment [h]	X	(X)							

Procedure	Screen [a]	Treatment	Treatment Assessment			Follow-up			
		(2 weeks max, each subject)	Safety Assessment Visit	Limited Safety Assessment Visit	EOT (excision)	*Unsched. Visits*	EOS [q]		Follow-up call
							Face	*Body*	
	Day -42 to -1	Day 1-3 of each Week (while lesion is not necrosed)	Day 4 of each Week (or 1 day after last lesion injection upon necrosis)	W2D1 or W3D1 (Part 2) [t]	Day 84-98 (or 12-14 wks from W1D1)		1 Week (7d±2) post excision [q]	2 Weeks (14d ±2) post excision [q]	30 Days post EOS with ongoing Aes [s]
Serum pregnancy test [i]	X		X				X	X	
Plasma immune response to VP-315 and T-cell clonality [j]	X				X				
Urine pregnancy test [k]		X							
Biopsy samples to dermatopathologist [l]	X								
Biopsy suture removal	X								
BCC Lesion count/location/measurement	X								
Physician Global Assessment [m]		X	X	X	X	X	X	X	
Cutaneous Reaction Assessment [m]		X	X	X	X	X	X	X	
Surgical excision tissue samples to dermatopathologist [n]					X				
PK sampling [o]		X							
Adverse events		X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X

Procedure	Screen [a]	Treatment	Treatment Assessment			Follow-up			
		(2 weeks max, each subject)	Safety Assessment Visit	Limited Safety Assessment Visit	EOT (excision)	*Unsched. Visits*	EOS [q]		Follow-up call
							Face	*Body*	
	Day -42 to -1	Day 1-3 of each Week (while lesion is not necrosed)	Day 4 of each Week (or 1 day after last lesion injection upon necrosis)	W2D1 or W3D1 (Part 2) [t]	Day 84-98 (or 12-14 wks from W1D1)		1 Week (7d±2) post excision [q]	2 Weeks (14d ±2) post excision [q]	30 Days post EOS with ongoing Aes [s]
Lesion photography [p]		X	X	X	X	X	X	X	
Patient-Reported Outcomes [q] (SCAR-Q & FACE-Q)			X		X				
Injection of VP-315		X							
Suture Removal and Postsurgical Assessment [r]							X	X	
Observer-Related Outcomes [u] (SCAR)					X				

BMI=body mass index; BP=blood pressure; EOS=end of study; EOT=end of treatment; HR=heart rate; PK=pharmacokinetic

a. Screening can occur up to 42 days prior to Study drug injection on Day 1. An IRB-approved ICF must be signed before any study specific procedures are performed.

b. Confirmation of eligibility criteria.

c. Vital signs (e.g., temperature, HR, BP) will be obtained at screening and at each treatment prior to application of study drug. Height and weight will be collected at Screening and EOS. Subjects must be supine for at least 5 minutes before BP and pulse rate measurements. On VP-315 dosing days, BP will be monitored serially just prior to injection, at 1, 3, and 5 minutes after each injection, and then every 5 minutes until 2 hours post last injection of the day using a manual/automated cuff system. For subjects in Part 2 (Cohorts 4 and 5 expansion groups), monitoring of BP *has* been decreased to 1-hour by the SRC following their safety meetings. An additional hour may be continued at the discretion of the PI.

d. Fitzpatrick Skin Type and lesion count.

e. Limited physical examination (dermatological exam). Symptom- or AE-directed physical examination may be performed if warranted. (See Source/CRF for further outline of assessment.)

f. Resting 12-lead ECGs (equipment provided by ECG Core Lab) will be recorded after the subject has been supine and at rest for at least 5 minutes at all visits, and prior to dosing on VP-315 dosing days. On VP-315 dosing days, 5-electrode Holter/telemetry (equipment provided by ECG Core Lab) will also be monitored continuously starting 15 minutes prior to injection and continuing 2-hours post last injection of the day. For subjects in Part 2 (Cohorts 4 and 5 expansion groups), Holter/telemetry monitoring *has* been decreased to 1-hour by the SRC following their safety meetings. An additional hour may be continued at the discretion of the PI. Note, in the event of EGC Core Lab equipment failure for the 12-lead ECG, sites may use their own 12-lead ECG machine and contact the ECG Core Lab for directions regarding upload to the study portal.

g. Clinical laboratory assessments to include a complete blood count and chemistry panel; samples will be collected at Screening, the Safety Assessment Visit, Unscheduled Visit and at the EOS (for subjects with excised lesions on both the face and the body, clinical laboratory samples will be collected only at the second EOS visit (i.e., at the EOS for Body; 2 weeks after excision). Local laboratory procedures and analysis should be used for these tests.

h. Blood samples for serum tryptase assessments will be collected at screening; additional samples will be collected as soon as possible following the occurrence of a hypersensitivity reaction, and again 60 to 120 minutes later.

i. Serum pregnancy test will be performed only on subjects of *childbearing potential* at all visits where other clinical laboratory tests are collected and at the EOS visit, prior to the subject being discharged from the study (Note: for subjects with excised lesions on both the face and the body, clinical laboratory samples and the serum pregnancy testing will be collected only at the second EOS visit [i.e., at the EOS for Body; 2 weeks after excision]).

j. Blood collected on a subset of subjects at screening and EOT visits. Approximately 3.0 mL will be collected in BD Vacutainer™ tubes with K2EDTA.

k. Urine pregnancy test will be performed prior to injection on Day 1 of each week only on subjects of *childbearing potential*.

l. If an eligible, *HISTORICAL* biopsy (shave or punch biopsy sample taken within 90 days prior to the W1D1 visit) is available in advance of subject screening, slides are to be submitted to the central dermatopathologist in accordance with the laboratory manual. If the subject has no *HISTORICAL* biopsy, shave or punch biopsy of the suspected BCC must be performed within t 90 days of W1D1. Shave biopsies will be performed according to standard of care to include superficial or middle papillary dermis. For punch biopsies,

a 2-mm biopsy will be collected for suspected BCC ≥0.5 cm to 1.0 cm, and 3-mm punch biopsy for suspected BCC >1.0 cm to 2.0 cm. Up to 5 suspected lesions may be biopsied. Punch biopsy sites should be closed with 1 to 2 non-absorbable sutures (sized 40 or 50) depending on investigator preference.

m. Physician's Global Assessment and Cutaneous Reaction Assessment will be performed prior to injection at all visits after Week 1 Day 1 for subjects in all parts of the study. The results of the Cutaneous Reaction Assessment are required in Parts 1 and 2 for evaluation of necrosis and DLTs.

n. Subjects will return for Follow-up Visits approximately 28-42 days (4-6 weeks) for Part 1 and 84-91 days (12 to 14 weeks) for Part 2 after receipt of first dose of VP-315 for excision of all BCC lesions (EOT).

o. Blood samples for PK assessments will be collected on the first day of full target dose administration immediately prior to the VP-315 dose and at 2- and 5-minutes post first injection and 2-, 5-, 10-, 20-, 30-, 60-, and 120-minutes post last injection; samples will also be collected on the following day 24 hours (±1 hour) post prior injection of VP-315. Blood samples for PK assessments will only be collected for subjects in Part 2 (Cohorts 4 and 5 expansion groups).

p. Photography of BCC lesion taken by a study team member prior to each treatment through EOS. Evaluation of lesion necrosis by the SRC (Part 1) or Medical Monitor (Part 2) is required for continued treatment.

q. Subjects in Part 2, will complete SCAR-Q and FACE-Q if they feel they have scars related to study treatment (relevant subscales only) at Safety Assessment Visits, and EOT.

r. Subjects will return approximately 7- or 14-days after excision (EOS) for a postsurgical assessment (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 EOS visits accordingly.

s. Subjects with AE(s) at the EOS visit will be contacted by phone at least 30 days after the EOS visit to confirm the status of any ongoing AE(s).

t. Limited Safety Assessment Visit conducted only in Part 2 –

    a. Cohorts 1-2: If the treated lesion is not fully necrosed at the W2D4 Safety Assessment Visit, a Limited Safety Assessemnt Visit should occur on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be adminstered.
    b. Cohorts 4-5 (including expansion groups): If only 1 target lesion is treated and complete necrosis is not achieved at the W1 Safety Assessment Visit, subjects should return on W2D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered. If a second target lesion was treated and complete necrosis is not achieved at the W2 Safety Assessment Visit, subjects should return on W3D1 for further evaluation of the lesion for necrosis. No additional treatment will be administered.

u. Scar Cosmesis Assessment and Rating (SCAR) Scale will be completed by the site investigator prior to excision at the EOS Visit.

8.4 Safety Assessments

8.4.1 Physical Examination

Limited physical examinations will include a dermatologic examination, including a Fitzpatrick Skin Type assessment (Screening only). Other systems will be examined as deemed necessary by the investigator depending on clinical signs and symptoms.

Screening Physical examination findings should be recorded on the medical and surgical history eCRF. Post-Screening limited physical examinations will be performed predose at each study visit. Additional physical examinations (limited or complete) may be performed as medically necessary, in the opinion of the investigator, and new findings recorded on the AE eCRF as appropriate.

Physical examinations will be performed at the EOT (excision) visit, 4 – 6 week (Part 1) and 12 to 14 weeks (Part 2) after the subject's first VP-315 treatment.

8.4.2 Vital Signs Data

Height and weight will be obtained at Screening and EOS.

Vital signs (e.g., body temperature, BP, and heart rate [HR]) will be obtained at all visits after the subject has been in the supine position for at least 5-minutes. Vital signs will be measured at the final evaluation during the EOS visit before the subject is discharged from the study.

On VP-315 dosing days, blood pressure will be monitored serially (observing for hypotension that meets the definitions as described in Section 10.1): just prior to injection, at 1-, 3-, and 5-minutes after each injection, and then every 5-minutes until 2 hours after the last injection of the day using a manual or automated cuff system (Table 8-1). For subjects in Part 2 – Cohorts 4 and 5 expansion groups, monitoring of BP has been decreased to 1-hour post treatment (an additional hour may be continued at the discretion of the PI).

8.4.3 Electrocardiograms

Subjects will be supine in a rested and calm state for at least 5 minutes before the ECG assessment is performed. ECG machines and Holter/telemetry will be provided by an ECG core lab, and these provided machines must be used for all study-related ECG requirements. Please note, in the event the provided 12-lead ECG machine (provided by the ECG core lab) is not functioning, the sites may utilize their own ECG machines and follow-up with the ECG core lab for uploading instructions. HR, QRS, QT, QTc, and PR intervals will be reported by the core lab.

Resting 12-lead ECGs will be recorded at the timepoints outlined in Table 8-1. On VP-315 dosing days, 5-electrode Holter/telemetry will also be monitored continuously starting 15 minutes prior to injection and 2 hours after the last injection of the day. For subjects in Part 2 Cohorts 4 and 5 expansion groups, Holter/telemetry has been decreased to 1-hour after the last injection of the day after receipt of the second daily dose of VP-315 (an additional hour may be continued at the discretion of the PI).

If a change in rhythm is detected during monitoring, the investigator will be notified by the central ECG core lab for evaluation of potential adverse events.

8.4.4 Clinical Laboratory Testing

A Clinical Laboratory Improvement Amendments (CLIA) certified [either central or local] laboratory will perform the clinical laboratory tests for this study as scheduled in Table 8-1. Tests are listed in Table 8-2 and will be performed at Screening, at each Safety Assessment Visit, at Unscheduled Visits and at the EOS; for subjects with excised lesions on both the face and the body, clinical laboratory samples will be collected only at the second EOS visit (i.e, at the EOS for Body).

Table 8-1
Clinical Laboratory Tests

Clinical Laboratory Tests	
Hematology: Red Blood Cell Count (RBC) White Blood Cell Count (WBC) w/ differential (absolute) Hematocrit Hemoglobin Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin Concentration (MCHC) Platelet Count	**Serum Chemistry:** Blood Urea Nitrogen (BUN) Creatinine SGOT (AST) SGPT (ALT) Lactic Dehydrogenase (LDH) Alkaline Phosphatase (ALP) Total Bilirubin Total Protein Albumin Glucose Calcium Sodium Chloride Potassium Bicarbonate
Pregnancy Test: (Only on subjects of childbearing potential) Serum β-hCG (Screening, Safety Assessment Visits, and EOS) Urine (prior to injection on Day 1 of each week)	**Serum tryptase**
T-Cell Clonality (Central lab only)	**Expansion Cohorts 4 and 5** **Serum Pharmacokinetics (PK) [Central lab only]**

EOS=end of study (visit); EOT=end of treatment (visit)

8.4.5 Serum Tryptase Assessment

Blood samples for serum tryptase assessments will be collected at screening; additional samples will be taken as necessary to monitor hypersensitivity reactions.

Blood samples will be collected in accordance with the National Institute for Health and Care Excellence clinical guideline 134 when any hypersensitivity reaction occurs (e.g., as soon as possible following the occurrence of a hypersensitivity reaction, and again 60 to 120 minutes

later). The actual collection time must be entered into the subject's record/source and transcribed accordingly.

8.4.6 Cutaneous Reaction Assessment

A CRA will be performed prior to injection at all visits after W1D1 (Appendix 1); the evaluation results are required for the evaluation of necrosis and DLTs. These local skin reactions will be collected independently of the adverse reactions to provide information on the specific types of reactions that can be expected to occur.

8.4.7 Pregnancy Testing

Serum β-human chorionic gonadotropin (β-hCG) pregnancy testing will be performed only on subjects of ***childbearing potential*** at all visits where clinical laboratory assessments are collected: Screening, Safety Assessment Visits, and at the EOS visit, prior to the subject being discharged from the study. For subjects with excised lesions on both the face and the body, serum pregnancy testing will be performed only at the second EOS visit (i.e., at the EOS for Body).

Urine pregnancy tests will be performed (only on subjects of ***childbearing potential***) prior to injection on Day 1 of each week; urine pregnancy tests must be confirmed negative prior to administration of VP-315. The results of these tests will be retained in the source document. In the event of a pregnancy, a Pregnancy Reporting Form must be completed and forwarded to the Sponsor (see Section 10.1.3.3 for additional information).

8.4.8 Pharmacokinetic Assessments

There will be no PK samples collected in Part 1.

In Part 2, a subset of up to 20 subjects in Cohorts 4 and 5 expansion group will have plasma PK samples obtained at the following timepoints on the first day of treatment with the full target dose:

- ***Predose***,
- 2- and 5- minutes ***post first injection***, and
- 2-, 5-, 10-, 20-, 30-, 60-, and 120-minutes ***post last injection***.
- Additional samples will be collected on the ***following day 24 hours (±1 hour) post Day 1 first injection*** of VP-315 ***(prior to Day 2 injection).***

All efforts should be made to collect samples as close to the protocol specified time point as possible. The actual collection time must be recorded in the subject's source documents and transcribed to the CRF.

8.5 Pharmacodynamic Assessments and Endpoints

8.5.1 Lesion Evaluation

At Screening, subjects will either provide a *HISTORICAL* biopsy (punch or shave) collected within the 90 days prior to the W1D1 visit or will undergo a punch or shave biopsy of the suspected BCC lesion within 90 days of W1D1. Shave biopsies will be performed according to standard of care and will include superficial or middle papillary dermis. For punch biopsies, a 2-mm punch biopsy will be collected for suspected BCC ≥0.5 cm to 1.0 cm, and a 3 -mm punch biopsy will be collected for suspected BCC >1.0 cm to 2.0 cm, up to 5 suspected lesions may be biopsied. All specimens (including *HISTORICAL* samples) will be formalin-fixed and paraffin embedded (FFPE) and H&E stained slides of specimen slices will be prepared and reviewed locally to determine eligibility. The H&E stained slides will be sent to the central lab for imaging and high quality images of the slides will be sent to the central dermatopathologist for confirmation of analysis/histology.

In accordance with the procedures noted in Table 8-1, all target and nontarget BCC lesions will be surgically excised with a 3 mm- margin 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after receipt of the W1D1 injection and tissue specimens preserved by FFPE. If a lesion has clinically cleared, the area where the lesion was will be excised accordingly. Both the screening and post-excision tissue blocks will be sent to the central lab for analysis of immune activation biomarkers including TILs by multiplexed IF-IHC, as well as for sequencing of genomic DNA from the lesion specimens to assess changes in T-cell receptor clonality.

During the study, subjects will be monitored for signs of efficacy—specifically, evidence of necrosis in the treated lesion(s).

8.5.2 Lesion Photography

Prior to each treatment, each safety visit, prior to excision and EOS, the treatment site, as well as any additional non-treated lesions that are to be followed, will be photographed, and assessed for the CRA. Site(s) will be provided with specialized equipment and training for consistent quality photographs. Photographs may be collected and stored on digital media.

Custom photographic equipment will be manufactured by Canfield for use in this study. Canfield will provide each site with a laptop computer with Canfield's proprietary Canfield Capture pre-installed on the equipment to guide site staff through all of steps of the image capture process required for this study. The software will be configured to include the specific visit schedule, image views and lighting modes to satisfy the needs of the study. In order to ensure consistent serial clinical photography is achieved during this study, all subject photographs will be reviewed (monitored) on an ongoing basis. Digital images will be transferred to Canfield via the secure website.

All images will be monitored for technical adherence to photographic protocol. Subject information, including site number, subject ID number, subject initials, and session date, will be entered into the database. The subject's F/U images will be technically reviewed compared to the baseline images. Photographic documentation will be carefully monitored to

assure that consistent serial photography will be achieved. Any subject images received that show identifying features (as defined by the Sponsor) will be digitally modified in an effort to protect the subject's identity. Image masking will occur where applicable during the monitoring process and a quality check will be completed before the images are available to view, download and print.

8.5.3 Subject-reported Outcomes

In Part 2 of the study, subject-reported outcomes will be collected with the SCAR-Q (Scar appearance, Scar symptoms, and Psychosocial impact scales) (Appendix 3) and relevant subscales of the FACE-Q (Appendix 4) (Satisfaction with outcome) completed at each Safety Assessment Visit, and EOT visit.

The FACE-Q will only be completed by subjects who have target or nontarget lesions on the face.

Brief instructions are provided at the start of each scale, and questionnaires will be administered via electronic Patient Reported Outcomes tablets during the subject visit in accordance with Table 8-1.

Each SCAR-Q and FACE-Q scale provides 4 response options that measure frequency. All scales use a 4-point scale. There is no overall or total score, only scores for each independent scale. Each scale is transformed into scores that range from 0 to 100. The scores are computed from the responses to the items by adding them together and converting the raw score to a scale from 0 to 100. Higher scores reflect a better outcome.

8.6 Observer-reported Outcomes

Scar Cosmesis Assessment and Rating (SCAR) Scale will be completed by the PI at the EOT visit, prior to the excision (Appendix 5). The scale includes six questions with six parameters scored by a clinician (scar spread, erythema, dyspigmentation, suture marks, hypertrophy/atrophy, overall impression) and two simple questions regarding symptoms (itch and pain) with yes/no answer options that are answered by the patient [Kantor, 2016].

8.7 Posttreatment Assessments

Approximately 4 to 6 weeks (Part 1) and 12 to 14 weeks (Part 2) after the first treatment with VP-315, subjects will return to the clinic for excision (3 mm margin) of all BCC lesions for histological evaluation.

A F/U visit will take place 1- or 2-weeks post excision (EOS visit). Suture removal and final photography should occur 7 (±1) or 14 (±2) days after excision (7 days on the face and 14 days on the body). Subjects with excised lesions on both the face and the body will be required to complete 2 EOS visits accordingly.

Subjects with AE(s) at the EOS visit will be contacted at least 30 days after the EOS visit by phone to confirm the status of any ongoing AE(s). The evaluations and/or procedures to be completed during EOT and EOS Visit are outlined in Table 8-1.

8.8 Assessment of the Immunological Response to VP-315 Treatment

In a subset of subjects, the anti-tumor immunological response to VP-315 treatment will be assessed in the excised tissue obtained from basal cell tumor biopsies performed at pre-screening (baseline) and at the approximate 12-24 -week post-treatment visit, as well as in peripheral blood samples acquired at the same time points. Analyses will include multiplexed immunofluorescence immunohistochemistry (IF-IHC) of slices from tumor tissue biopsies as well as assessment of T-cell clonality in both peripheral blood and in the same tissue obtained from the tumor biopsies.

8.8.1 Multiplexed Immunofluorescence Immunohistochemistry

Tissue sections from the formalin-fixed, paraffin-embedded (FFPE) tissue from pre- and post-treatment biopsy samples will be analyzed by multiplexed IF-IHC using fluorescent staining using a panel of 8 markers to identify tumor infiltrating lymphocyte (TIL) T-cell subsets and changes in immune activation.

8.8.2 Assessment of T-cell Clonality

The adaptive immune response to basal cell tumor antigens released following VP-315 treatment will be assessed by measuring T-cell clonal expansion in peripheral blood and the repertoire of T-cell clones infiltrated into the tumor tissue microenvironment using a highly sensitive next-generation T-cell receptor sequencing assay. gDNA for the assay will be obtained from the same FFPE tissue blocks used for the multiplexed IF-IHC described in Section 8.7.1 and from peripheral blood samples (3.0 mL) collected in BD Vacutainer™ tubes with K_2EDTA at the screening and approximate 12-week post-treatment visits.

9. REMOVAL AND REPLACEMENT OF SUBJECTS

9.1 Removal of Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from protocol required procedures or from the study as a whole at any time prior to study completion.

Withdrawal of consent from the study means that the subject does not wish to undergo further protocol-required procedures, and the subject does not wish—or is unable—to continue further study participation. Subject data up to the withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal from the study include any of the following:

- subject request (withdrawal of consent)
- safety concern (e.g., due to an AE, ineligibility determined, protocol deviation, noncompliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- decision by sponsor (other than subject request or safety concern)
- loss to F/U

In the event of a premature withdrawal from the study, the subject should attend an EOS visit when possible, and the investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

9.2 Replacement of Subjects

Subjects who withdraw or are removed from the study for reasons other than DLT will be replaced to achieve the required number of evaluable subjects. Identifying subject numbers will not be reused; all newly enrolled subjects will have a unique subject identification number.

10. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

10.1 Adverse Events

10.1.1 Definition of Adverse Events

Consistent with the US Code of Federal Regulations (CFR), Title 21 §312.32, an AE is defined as any untoward medical occurrence associated with the use of an investigational product, regardless of its causal relationship to the investigational product.

The investigator is responsible for ensuring that any AEs observed by the investigator (or staff) or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome.

Treatment-emergent adverse events (TEAE) include all AEs that occur during the treatment period (i.e., W1D1 through EOS).

Treatment-related adverse events (TRAE) include all AEs that occur during the treatment period (W1D1 through EOS) that the PI determines is related to the investigational agent/procedure.

Treatment-related adverse events of special interest (TRAE SI) will be reported in Part 2 of the study. A treatment-related adverse event of special interest (TRAE SI) will be defined as any one of the VP-315 related adverse events (AE) that occurs during the treatment visit listed in Section 10.2.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered to be AEs.

10.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all AEs (i.e., those observed by the investigator [or staff] or reported by the subject) with an onset occurring any time between the subject providing the signed ICF through the completion of the F/U Visit are reported on the AE Summary eCRF.

The investigator is required to assign the following AE attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution
- severity
- assessment of relatedness to study drug
- action taken

The investigator may be asked to provide F/U information, discharge summaries, and extracts from medical records or eCRFs.

In Part 1 of the study, the AE grading scale used will be the CTCAE v5.0. The relationship of the AE to the investigational product will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?". The investigator should respond to this question with either Yes or No.

If the AE occurred before VP-315 treatment, the relationship of the AE to study screening is to be assessed by means of a similar question: "Is there a reasonable possibility that the event may have occurred because of study screening?" The investigator should respond to this question with either Yes or No. If the answer is Yes, record what part of the study screening is suspected.

Medically significant AEs considered by the investigator or Sponsor to be related to VP-315 will be followed until resolved or considered stable. The outcome of each AE must be recorded according to the following classification: unknown, completely resolved, resolved with sequelae, ongoing, death.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as AEs; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered AEs.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. A subject, or subject's legal guardian, can also voluntarily withdraw from treatment due to an AE. If the subject withdraws consent, the subject is encouraged to attend, at a minimum, the EOS visit (Table 8-1).

10.1.3 Serious Adverse Events

10.1.3.1 Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect, and/or
- other significant medical hazard

An AE would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (e.g., overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias.

10.1.3.2 Reporting Procedures for Serious Adverse Events

Serious adverse events will be collected and recorded at least throughout the study period, beginning with the signing of the informed consent through 30 days after the last dose of investigational product or last subject visit, whichever is longer.

It is required that any SAE, regardless of its investigator-determined causal relationship to study drug, be reported to the Sponsor Medical Monitor within 1 working day of discovery or notification of the event. Each principal investigator will be provided with a Serious Adverse Event Report Form prefilled with the name, telephone number, and fax number of the local Sponsor Global Safety contact.

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to investigational product will be collected and reported within 1 working day of discovery or notification of the event.

Follow-up SAE information should be provided by the investigator as appropriate until the SAE has resolved. The investigator is obligated to answer queries and to submit requested F/U information for any SAE until the case is considered closed by the Sponsor Medical Monitor or designee.

The investigator should notify the appropriate IRB or ethics committee of SAEs occurring at the site and other AE reports received from Sponsor, in accordance with local procedures and statutes.

10.1.3.3 Pregnancy Reporting

Pregnancies are not considered SAEs; however, any pregnancy complication or an induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Sponsor.

The investigator **must** report any pregnancies to the Sponsor's Medical Monitor (using the Pregnancy Reporting Form) within 24 hours of the initial report of a male subject's female partner or female subject becoming pregnant during the course of the study. Any pregnancies that occur within the 30 days following the last investigational medicinal product dose should also be reported.

Monitoring of the subject should continue until the conclusion of the pregnancy. Additional information regarding the pregnancy should be submitted to the Sponsor on the Pregnancy Form. The outcome should be reported to the Sponsor using the Pregnancy Outcome Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to the Sponsor.

10.2 Dose-limiting Toxicity/Treatment-related Adverse Event of Special Interest

For Part 1 of the study, a dose limiting toxicity (DLT) is defined as any of the following VP-315 related adverse event (AE) that occurs during the DLT period:

For Part 2 of the study, a treatment-related adverse event of special interest (TRAE SI) will be defined as any on the following VP-315 related adverse (AE) that occurs during the treatment visit:

Hypotension meeting any of the following definitions:

- >20 mmHg decrease in systolic BP with absolute systolic BP <100 mmHg, or
- >20 mmHg decrease in systolic BP with clinical symptoms, or
- absolute diastolic BP <60 mmHg

- Significant elevation of serum tryptase concentration is defined as an increase of 1.2× baseline plus 2
- Any Grade 2 or higher AE occurring between start of dose administration and the end of the postdose observation period on any given treatment day
- Any Grade 2 or higher AE considered by the investigator to be related to the investigational product
- Any Grade 2 or higher local reactogenic AE (injection-site pain, erythema, induration)
- Any Grade 2 or higher systemic reactogenic AEs (fever, myalgia, headache)

Any subject who experiences a DLT/TRAE SI will receive no further VP-315.

If the DLT/TRAE SI is caused by an unexpected drug-related event that is not listed in the consent form, Sponsor will revise the consent form appropriately and submit it to the IRB. All subjects will be advised of the new toxicity and their willingness to continue on study will be confirmed. When the amended consent form is approved by the IRB, all subjects remaining on the study will be asked to sign the amended consent form.

11. STATISTICAL CONSIDERATIONS

11.1 General Considerations

A statistical analysis plan (SAP) will be provided that gives a complete description of the statistical methods to be used in this study. The SAP will describe the methods and data presentation to be used for the analysis of safety, efficacy, and PK outcome data. If analyses in the SAP do not align with the analyses described here, the SAP will identify where those methods differ.

Analyses will be carried out by study part (Part 1 and Part 2). For Part 1 and Part 2, an overall summary will be provided. More detail will be provided in the SAP.

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviations, median, minimum, and maximum. Counts and percentages will be provided for categorical/ordinal variables. Unless specified otherwise, denominators for percentages will only consider non missing responses. For any summaries that involve change from baseline, baseline will be defined as the last measurement obtained prior to first injection of study drug. By-subject listings for all subjects will be provided for data collected.

11.2 Sample Size Considerations

The sample size determination is not based on statistical power considerations, as the primary objective of this study is the assessment of safety and tolerability. However, the number of subjects enrolled in each study part should be adequate to meet the safety objectives and to provide preliminary evidence of efficacy.

11.3 Analysis Populations

The following populations will be used for the VP-315 study:

- The Safety Population will include all subjects who take at least 1 dose of VP-315. Safety analyses will be conducted using the Safety Population.
- Full Analysis Set (FAS): this set is a subset of all enrolled subjects, excluding subjects who do not receive at least 1 full dose of VP-315 and those with no assessment of histologic clearance. The FAS will serve as the primary population for the analysis of efficacy-related data.
- Per-protocol Analysis Set (PPS): this set is a subset of the FAS, excluding subjects with important protocol deviations that may substantially affect the results of the primary efficacy analyses. The final determination on protocol violations, and thereby the composition of the PPS, will be made before clinical database lock. The PPS may be used for supportive analyses.
- PK Analysis Set: this set consists of subjects in the Safety Population with at least 1 plasma sample with quantifiable concentration of VP-315.

11.4 Study Endpoints

11.4.1 Safety Endpoints

The safety endpoints associated with study objectives for the VP-315 study include the following:

- (Part 1, Part 2) Discontinuation due to AEs
- (Part 1) Occurrence of DLTs
- (Part 1, Part 2) CRAs
- (Part 2) TRAEs
- (Part 2) TRAE SIs
- (Part 2) Serious TRAEs

11.4.2 Efficacy Endpoints

Efficacy endpoints associated with study objectives for the VP-315 study include the following:

- (Part 2 Cohorts 4 and 5) Complete clearance of treated lesions at excision
- (Part 1, Part 2) Histologic clearance of treated lesions at excision
- (Part 1, Part 2) Clinical clearance of treated lesions at excision
- (Part 1, Part 2) Estimate of remaining tumor volume at excision (necrotic cells:tumor cells)
- (Part 1, Part 2) Abscopal effect based on nontreated lesions at excision
- (Part 1, Part 2) PGA
- (Part 2) SCAR-Q, FACE-Q

11.4.3 Pharmacokinetic Endpoints

Blood samples for PK assessments will only be collected for subjects in Part 2 (Cohorts 4 and 5 expansion groups) of the study. Pharmacokinetic endpoints of this study are to characterize the plasma PK parameters of VP-315 and its metabolites following multiple doses of VP-315; standard noncompartmental methods will be used.

11.4.4 Exploratory Endpoints

Tumor tissue samples from the pre-treatment screening biopsies and from the post-treatment excised tumor tissue will undergo multiplexed IF-IHC and changes in the expression of a panel of 8 immune markers in response to the treatment will be analyzed. Additionally, genomic DNA will be isolated from the same tissue samples, as well as from peripheral blood samples collected at the same pre- and post-treatment time points and will undergo sequencing and analyzed for changes in T-cell receptor clonality.

11.5 Analysis Methods

11.5.1 Subject Characteristics and Disposition

Descriptive summaries of demographic and baseline characteristics for all enrolled subjects will be tabulated by study part. The number of subjects included in each analysis population will be summarized, along with the reason for exclusion from any analysis populations. Subjects discontinuing from study drug or withdrawing from the study and the primary reason for discontinuation/withdrawal will be summarized.

11.5.2 Safety Analyses

All subjects who receive any amount of study drug will be included in the safety analysis. Safety will be evaluated by study part.

All AEs will be coded using the MedDRA dictionary. Tabular summaries of AEs will only consider treatment-emergent adverse events (TEAEs), which are defined as those AEs with a start date on or after first dose of study drug. The incidence of TEAEs will be summarized by system organ class (SOC), preferred term (PT), relationship to study drug, and severity. Serious TEAEs will be summarized by SOC and PT. TEAEs leading to discontinuation as well as TEAEs identified as dose limiting toxicities will be listed and summarized if sufficient counts of either are reported.

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range). In addition, a change from baseline will be presented. Standard shift tables will also be prepared presenting toxicity grade vs baseline.

Vital signs and ECG results will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values. Change from baseline for vital signs and ECG parameters will also be summarized. For ECG parameters, both QTcB (Bazett's correction) and QTcF (Fridericia's correction) will be displayed.

Cutaneous Reaction Assessments will be summarized using counts and percentages for each severity level (none, mild, moderate, severe). Separate summaries will be presented for each cutaneous reaction type and visit.

11.5.3 Efficacy Analyses

Efficacy analyses will be conducted for all lesions of all subjects enrolled in the study and carried out by study part.

Complete clearance will be summarized using counts and percentages. Histological clearance and clinical clearance will be summarized using similar methods. Other efficacy endpoints to be summarized include estimates of tumor volume, abscopal effect on nontreated lesions, PGA, SCAR-Q (Part 2 and 3 only) and FACE-Q (Part 2 and 3 only). Each endpoint will be summarized as described in Section 11.1, based on the type of data collected.

11.5.4 Pharmacokinetic Analyses

Blood samples will be collected on the first day of dose administration immediately prior to the VP-315 dose and at 2-and 5-minutes post first injection, and 2-, 5-, 10-, 20-, 30-, 60-, and 120-minutes post last injection. Additional samples will we collected at 24 (±1) hours post-dose prior to administration of the next VP-315 dose. Blood samples for PK will only be collected for subjects in Part2 (Cohorts 4 and 5 expansion groups) of the study.

Concentrations of VP-315 and metabolites will be determined in plasma using a validated bioanalytical assay(s). Individual subject VP-315 concentration-time data will be displayed using scheduled sampling times. Descriptive statistics (e.g., n, mean, SD, %CV, median and range) will be calculated for each sampling time. Plasma concentrations of the study drug over time will be plotted in semilogarithmic and linear formats as mean ± SD. Plasma concentration-time data for each subject will be analyzed using standard noncompartmental methods. Plasma PK parameters of VP-315 and metabolites will include C_{max}, T_{max}, $AUC_{0\text{-}last}$, and AUC_{inf}.

Dose proportionality information will be obtained by comparing plasma levels of VP-315 across all dose levels. The primary method for evaluation of dose proportionality will be based on $AUC_{0\text{-}last}$, AUC_{inf}, AUC_{tau}, and C_{max}. The population mean slope will be estimated with a 90% CI. An alternate evaluation of dose proportionality will be conducted using ANOVA on dose-normalized $AUC_{0\text{-}last}$, AUC_{inf}, and C_{max}. The analysis will be conducted on log-transformed data. The model will include dose as a fixed effect and subject as random effect. Calculations of the 90% CI for the ratio of dose comparisons will be constructed.

Descriptive statistics for VP-315 PK concentrations will be tabulated at each scheduled timepoint by cohort. Statistics for PK concentrations will include the number of subjects, mean, standard deviation, CV%, median, minimum, maximum, geometric mean, and geometric CV%.

Descriptive statistics for VP-315 PK parameters will be provided for Cohorts 4 and 5 expansion subjects in Part 2. Summaries will include the number of subjects, mean, standard deviation, CV%, median, minimum, maximum, geometric mean, and geometric CV% (where applicable).

12. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

12.1 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized representative, and investigators abide by Good Clinical Practice (GCP) as described in International Council for Harmonisation (ICH) guideline E6(R2), and in 21 CFR parts 11, 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the most recent revision of the Declaration of Helsinki (October 2013) that is recognized by the US Food and Drug Administration (FDA), the European Medicines Agency, and other regulatory agencies.

12.2 Informed Consent

A template ICF will be provided by the Sponsor or designee. According to the Protection of Human Subjects regulations listing in 21 CFR Part 50, the ICF must be reviewed and approved by the IRB and must contain all elements required, as applicable, by national or local laws/regulations or requirements, US FDA regulations or regulations of the authority having jurisdiction over the location in which the study is being conducted, and institutional policies. If, during the approval process, the IRB makes any substantive changes to the ICF, then this altered ICF must be provided to the Sponsor or designee for review before it is implemented.

All subjects will be provided with the approved written ICF for this study, which will provide sufficient information for the subject to make an informed decision about participation in this study and to facilitate comprehension of the information. Each subject will be provided adequate opportunity to ask questions and to consider whether to participate. The investigator is responsible for obtaining the potential subject's voluntary agreement to participate, and to continue providing information as the clinical study progresses or as the subject or situation requires.

Voluntary informed consent must be obtained from each eligible subject before any protocol-defined procedures are performed. The subject's signature on the ICF indicates his/her willingness to participate in this study. Other study personnel (e.g., Principal Investigator, Study Nurse) will sign the ICF in accordance with local procedures.

12.3 Institutional Review Board

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be received by Sponsor before recruitment of subjects into the study and shipment of VP-315.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Sponsor, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Sponsor.

12.4 Subject Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the sponsor and its authorized representatives are allowed full access to the records.

All study subjects must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection laws. The types of disclosure must also be explained to the subject, who will be required to be informed about how their data will be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs shall be by unique subject identification numbers (such as screening number) only. All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the Sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff.

12.5 Investigator Signatory Obligations

The investigator is to sign each clinical study report.

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except when necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the Sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the ICF. The IRB must be informed of all amendments and give approval prior to their implementation. The Sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator updated as detailed in the ICH GCP guidelines. The amendment must be signed by the investigator and approved prior to implementation, except if amendments are issued to eliminate an immediate hazard(s); in such case the amendment may be retrospectively approved. The investigator should not implement a change to the protocol without prior review and documented approval/favorable opinion of the IRB of an amendment, except where to eliminate an immediate hazard(s) to the study subjects.

Where only administrative changes are required to the protocol, the IRB will be notified for informational purposes only.

Sponsor reserves the right to terminate the study at any time. Both Sponsor and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB in writing of the study's completion or early termination (ET) and send a copy of the notification to Sponsor.

13.2 Study Documentation and Archive

The Principal Investigator shall retain all study-related documentation, including source data, source documents, eCRFs, laboratory and diagnostic results, protocol and amendments, study drug accountability records, regulatory documentation and correspondence, ICFs, patient identification lists, and correspondence. These records should be retained in the format they were originally obtained (e.g., electronic or paper) unless a quality controlled and authorized complete electronic version is created for long-term storage at the end of the study. The Sponsor will provide an electronic copy of the final eCRF for each study subject within 3 months of study closeout.

The investigator must retain an organized file with all study-related documentation that is suitable for inspection by the Sponsor and representatives of Regulatory Authorities.

The investigator shall retain all study records for the longer of 1) 2 years after the last marketing authorization for the investigational product has been approved or Sponsor has discontinued research on the investigational product, and 2) such longer period as required by regulatory requirements.

Documents should be stored in such a way that they can be accessed, and data can be retrieved at a later date. Consideration should be given to security and environmental risks.

Documentation retention will generally comply with Section 8 of the ICH consolidated guideline on GCP, Essential Documents for the Conduct of a Clinical Trial.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator, or the Research Site should the investigator leave the institution. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor prior to any actions being taken.

13.3 Study Monitoring and Data Collection

Clinical research associates (CRAs) representing the Sponsor will routinely visit the study site or develop a remote monitoring strategy throughout the study. The investigator will ensure that the monitor, or other compliance or quality assurance reviewer, is given access to all study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, medical records), and, if the visit occurs on site, has adequate space to conduct the monitoring visit. In addition to the monitoring visits, frequent communications (email, letter, telephone, and/or fax) by the CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements. The investigator, or appropriate designee, will allocate adequate time for monitoring activities and F/U correspondences.

The CRA will review ICFs, eCRFs, and laboratory and other diagnostic reports, comparing them with source documents to verify adherence to the protocol, and to ensure complete, accurate, consistent, and timely collection of data. The CRA will record and report any protocol deviations not previously sent to the Sponsor. The CRA will also confirm that AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB. The investigator will be asked to provide any missing information or to clarify any discrepancies found by the CRA. For on-site monitoring visits, it is expected that the investigator will be present for a concluding review at the end of each monitoring visit. Remote monitoring may be done if feasible, per the Monitoring Plan.

13.4 Publication Policy

This study will be registered at ClinicalTrials.gov and after study completion, results information from this study will be posted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Publication of the results by the investigator will be subject to mutual written agreement between the investigator and the Sponsor or determined by the publication/steering committee prior to preparation of the publication.

14. REFERENCES

Adalsteinsson JA, Ratner D, Olafsdóttir E, et al. Basal cell carcinoma: an emerging epidemic in women in Iceland. British Journal of Dermatology. 2020;183(5):847-856.

American Academy of Dermatology Association (AAD). Skin Cancer; Incidence Rates. Accessed 01 February 2021. https://www.aad.org/media/stats-skin-cancer

Camilio KA, Berge G, Ravuri CS, Rekdal O, Sveinbjørnsson B. Complete regression and systemic protective immune responses obtained in B16 melanomas after treatment with LTX-315. Cancer Immunol Immunother. 2014;63(6):601-613.

Diffey B, Langtry J. Skin cancer incidence and the ageing population. British Journal Of Dermatology. 2005;153(3):679-680.

Forveille S, Zhou H, Sauvat A, et al. The oncolytic peptide LTX-315 triggers necrotic cell death. Cell Cycle. 2015;14(21):3506-3512.

Goldenberg G, Karagiannis T, Palmer JB, et al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: A retrospective cohort study. Journal of the American Academy of Dermatology. 2016;75(5):957-966.e2.

Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002−2006 and 2007−2011. American Journal of Preventive Medicine. 2015;48(2):183-187.

Hancock RE. Cationic peptides: effectors in innate immunity and novel antimicrobials. Lancet Infect Dis. 2001;1(3):156-164.

Jebsen NL, Apelseth TO, Haugland HK, et al. Enhanced T-lymphocyte infiltration in a desmoid tumor of the thoracic wall in a young woman treated with intratumoral injections of the oncolytic peptide LTX-315: a case report. J Med Case Rep. 2019;13(1):177.

Kantor, J. The SCAR Scale (Scar Cosmesis Assessment and Rating Scale): Development and validation of a new outcome measure for postoperative scar assessment. British Journal of Dermatology. 2016;175(6), pp1394-1396.

Karimkhani C, Boyers LN, Dellavalle RP, Weinstock MA. It's time for "keratinocyte carcinoma" to replace the term "nonmelanoma skin cancer." J Am Acad Dermatol. 2015;72(1):186-187.

Liao H-W, Garris C, Pfirschke C, et al. LTX-315 sequentially promotes lymphocyte-independent and lymphocyte-dependent antitumor effects. Cell Stress. 2019;3(11):348-360.

Madan V, Lear JT, Szeimies R-M. Non-melanoma skin cancer. The Lancet. 2010;375(9715):673-685.

Nestvold J, Wang M-Y, Camilio KA, et al. Oncolytic peptide LTX-315 induces an immune-mediated abscopal effect in a rat sarcoma model. Oncoimmunology. 2017;6(8):e1338236.

Papo N, Shai Y. Host defense peptides as new weapons in cancer treatment. Cell Mol Life Sci. 2005;62(7-8):784-790.

Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the US Population, 2012. JAMA Dermatol. 2015;151(10):1081.

Skin Cancer Foundation. Skin Cancer Facts and Statistics. Accessed 01 February 2021. https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/

Spicer J, Marabelle A, Baurain J-F, et al. Safety, Antitumor Activity, and T-cell Responses in a Dose-Ranging Phase I Trial of the Oncolytic Peptide LTX-315 in Patients with Solid Tumors. Clin Cancer Res. 2021;27(10):2755-2763.

Sveinbjørnsson B, Camilio KA, Haug BE, Rekdal Ø. LTX-315: a first-in-class oncolytic peptide that reprograms the tumor microenvironment. Future Med Chem. 2017;9(12):1339-1344.

Wu S, Han J, Li W-Q, Li T, Qureshi AA. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. Am J Epidemiol. 2013;178(6):890-897.

Zasloff M. Antimicrobial Peptides in Health and Disease. New England Journal of Medicine. 2002;347(15):1199-1200.

15. APPENDICES

Appendix 1
Cutaneous Reaction Assessment*

Evaluate the tissue condition at the treatment site for the presence and severity of each of the following cutaneous reactions.

	Target Lesions		Nontarget Lesions		
Reaction	**Lesion 1**	**Lesion 2**	**Lesion 1**	**Lesion 2**	**Lesion 3**
Erythema	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Induration	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Swelling	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Blister Formation	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Desquamation	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe

Evaluate the tissue condition at the treatment site for the presence and severity of each of the following cutaneous reactions.

Reaction	Target Lesions		Nontarget Lesions		
	Lesion 1	**Lesion 2**	**Lesion 1**	**Lesion 2**	**Lesion 3**
Erosion	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Ulceration	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe
Necrosis	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe	☐ none ☐ mild ☐ moderate ☐ severe

Orenberg EK, Miller BH, Greenway HT, et al. The effect of intralesional 5-fluorouracil therapeutic implant (MPI 5003) for treatment of basal cell carcinoma. J Am Acad Dermatol. 1992;27(5 Pt 1):723-728.

***Complete the assessment for each reaction and for any reaction that is Mild, Moderate or Severe enter event on the Adverse Event Page**

Appendix 2
Physician's Global Assessment

Global Assessment of Improvement

Target Lesions	
Lesion 1	**Lesion 2**
☐ 100% improvement, no visible tumor	☐ 100% improvement, no visible tumor
☐ 75% to <100% improvement	☐ 75% to <100% improvement
☐ 50% to <75% improvement	☐ 50% to <75% improvement
☐ 25% to <50% improvement	☐ 25% to <50% improvement
☐ up to 25% improvement	☐ up to 25% improvement
☐ no change	☐ no change
☐ worse	☐ worse

Nontarget Lesions		
Lesion 1	**Lesion 2**	**Lesion 3**
☐ 100% improvement, no visible tumor	☐ 100% improvement, no visible tumor	☐ 100% improvement, no visible tumor
☐ 75% to <100% improvement	☐ 75% to <100% improvement	☐ 75% to <100% improvement
☐ 50% to <75% improvement	☐ 50% to <75% improvement	☐ 50% to <75% improvement
☐ 25% to <50% improvement	☐ 25% to <50% improvement	☐ 25% to <50% improvement
☐ up to 25% improvement	☐ up to 25% improvement	☐ up to 25% improvement
☐ no change	☐ no change	☐ no change
☐ worse	☐ worse	☐ worse

Orenberg EK, Miller BH, Greenway HT, et al. The effect of intralesional 5-fluorouracil therapeutic implant (MPI 5003) for treatment of basal cell carcinoma. J Am Acad Dermatol. 1992;27(5 Pt 1):723-728.

Appendix 3
SCAR-Q

The SCAR-Q© is a rigorously developed patient-reported outcome (PRO) instrument that can be used to collect and compare evidence-based outcomes data from children and adults aged 8 years and older with a surgical, traumatic, or burns scar.

http://qportfolio.org/wp-content/uploads/2020/02/SCAR-Q-USERS-GUIDE-V1.pdf

Appendix 4
FACE-Q

The FACE-Q© is a PRO measure that can be used to measure outcomes of aesthetic facial procedures and products from the patient's perspective. The FACE-Q© can be used to measure outcomes for any type of surgical or minimally invasive facial aesthetic treatment. This PRO instrument has been used to evaluate the safety and effectiveness of facial aesthetic treatments in numerous clinical trial settings and to inform patient care in clinical practice. The FACE-Q© is composed of a set of 39 independently functioning scales/checklists that measure 3 overarching domains: Facial Appearance, Health-Related Quality of Life, and Adverse Effects. These domains form the basis of the FACE-Q© conceptual framework (see link below). The FACE-Q© modular approach means that only the subset of scales most relevant to a specific research objective or clinical patient population need be administered.

http://qportfolio.org/wp-content/uploads/2020/02/FACE-Q-AESTHETICS-USER-GUIDE-V1.pdf

Appendix 5
Scar Cosemesis and Rating Scale (SCAR)

Clinician Items	Scale Ratings
Scar spread	0, None to near-invisible
	1, Pencil-thin line
	2, Mild spread, noticeable on close inspection
	3, Moderate spread, obvious scarring
	4, Severe spread
Erythema	0, None
	1, Light pink, some telangiectasias may be present
	2, Red, many telangiectasias may be present
	3, Deep red or purple
Dyspigmentation (includes hyperpigmentation and hypopigmentation)	0, Absent
	1, Present
Track marks or suture marks	0, Absent
	1, Present
Hypertrophy/atrophy	0, None
	1, Mild: palpable, barely visible hypertrophy or atrophy
	2, Moderate: clearly visible hypertrophy or atrophy
	3, Severe: marked hypertrophy or atrophy or keloid formation
Overall impression	0, Desirable scar
	1, Undesirable scar
Patient items	
Have you been bothered by any itch from the scar in the past 24 h?	0, No
	1, Yes
Have you been bothered by any pain from the scar in the past 24 h?	0, No
	1, Yes
Total score range	0 (best possible scar) to 15 (worst possible scar)