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Document Title:	Amendments to the Clinical Investigation Plan for the BIO|CONCEPT.Amvia Study
Document Version and Date:	CIP amendment 01, 10-Feb-2023 CIP amendment 02, 13-Mar-2023
ClinicalTrials.gov Identifier:	NCT05610176

CIP Amendment 1

for the

BIO|CONCEPT.Amvia

First in Human study for the Amvia/Solvia pacemaker family

Applicable for all participating clinical sites

Clinical investigation plan: 1-0 of 30-May-2022
Reference number: BA115
Amendment version: CIP Amendment 1, version 1-0 of 10-Feb-2023

Amendment history

Title	Scope	Key words	Date	Status
N/A	(no previous amendments)	N/A	N/A	N/A

The amendment comprises the following changes:

1) The new programmer software version NEO 2301.A/S is introduced into the study to replace the previous version NEO2204.A/S. The new software version includes several improvements: automatic pseudonymization of patient data in the software user interface and exports, implementation of the `ReportShare´ export function and enhanced touchscreen reaction time. A falsely reported alarm in the Home Monitoring Service Center (HMSC) about the deactivation of the aATP feature will also be corrected within the new software version. The new software supports interrogation of the study devices as well as market-approved devices.

The Amendment is a standalone document in addition to the existing CIP version 1-0. Please refer to the table below for all details of the changes.

Previous CIP	Modification
Sections 2, 4 and 8: Throughout the study protocol the programmer software is referred to as `NEO 2204.A/S´	Throughout the document, wherever the programmer software is referenced, 'version NEO 2301.A/S and subsequent versions' is added. The version NEO 2301.A/S is intended to replace version NEO2204.A/S, but both versions may be in use until the amendment is approved by all Ethics Committees.
Section 6.5 describes steps to control or mitigate risks in the clinical investigation.	To avoid the accidental use of the study programmer software outside of the study, the relevant device accountability measures apply. Additionally, study programmer devices will be equipped with a striking label to point out the restriction 'exclusively for clinical investigation'.

This amendment is substantial according to ISO 14155 section 5.6.4 e).

Coordinating Investigator

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Date

Signature

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CIP Amendment 2

Non-substantial

for the

BIO|CONCEPT.Amvia

First in Human study for the Amvia/Solvia pacemaker family

Applicable for all participating clinical sites

Clinical investigation plan: 1-0 of 30-May-2022
Reference number: BA115
Amendment version: CIP Amendment 2, version 1-0 of 13-Mar-2023

Amendment history

Title	Scope	Key words	Date	Status[1]
Amendment 1	ALL sites	Introduction of new programmer software version NEO 2301.A/S	10-Feb-2023	Pending

[1] Status might be 'applicable', 'expired', 'withdrawn' or 'obsolete'

1) Fixed distribution of device types lifted

The requirements for minimum numbers of device types and activation of specific features are lifted in order to avoid a potential slow-down of enrollment at the end of the enrollment phase. These numbers were initially defined to ensure that not only one device type that doesn´t incorporate the features of interest is implanted predominantly. The current distribution of devices shows a good profile, so that these limitations can be omitted. The investigators shall however be encouraged to activate the features CRT AutoAdapt and atrial ATP (aATP) in all eligible patients at their discretion.

2) Activation of atial ATP without history of atrial arrhythmias

The activation of aATP shall no longer be restricted to patients with known history of atrial arrhythmias, as these patients were rarely enrolled up to now. The feature may be activated in all DR-T and HF-T QP patients at the investigators' discretion to allow for observation of the feature's functioning and assessment of usability and programmability, even though the delivery of therapies in these patients is improbable. If a patient without history of atrial arrythmias does not develop any arrythmia, no treatment will be delivered. However, if such a patient does have any stable atrial arrhythmia over the course of time, they might benefit from the treatment from the very first episode onward.

The Amendment is a standalone document in addition to the existing CIP version 1-0 and CIP amendment 1.

Previous CIP	Modification
Synopsis / Sample size: 50, thereof: • 10-15 single-chamber • Min. 10 dual-chamber • Min. 10 triple-chamber • Min. 10 with aATP ‚ON' • Min. 5 with CRT AutoAdapt ‚ON'	Deletion of required numbers per device type or feature
8.1.3.3 Further data of interest • Usage and assessment or CRT AutoAdapt ('ON' in at least 5 patients; HF-T QP only) • Usage and assessment of atrial ATP (aATP 'ON' in at least 10 pts.; DR-T or HF-T QP only)	Deletion of ` 'ON' in at least 5 patients' and 'aATP 'ON' in at least 10 pts'
8.2.3 Number of investigational devices to be used and a justification Within the 50 patients to be enrolled, the distribution of the different types of devices is planned as follows: • 10-15 Amvia Sky SR-T • Min. 10 Amvia Sky DR-T • Min. 10 Amvia Sky HF-T QP	Change 'is planned' to ‚should be' Add: 'However, this planned distribution of devices should not prolong the enrollment period in case that one or two of the device sub-groups are not completed within the planned enrollment period. Therefore, the device types may be mutually substituted.'
8.1.4.9 Assessment of CRT AutoAdapt CRT AutoAdapt shall be programmed 'ON' in at least five patients with CRT-P devices in the study. However, its use is recommended for all CRT-P patients, with the exception of patients with AV block, for whom this feature is contraindicated. Furthermore, CRT AutoAdapt cannot be programmed at the same time as atrial ATP.	Deletion of the paragraph. Replace with 'Investigators are encouraged to program CRT AutoAdapt 'ON' in all patients with CRT-P devices, with the exception of patients with AV block, for whom this feature is contraindicated.'
8.1.4.10 Assessment of atrial ATP It is required that atrial ATP is programmed 'ON' in at least 10 patients with dual or triple chamber devices and a known history of atrial arrhythmias except permanent atrial fibrillation. (…). However, atrial ATP cannot be programmed at the same time as CRT AutoAdapt.	Deletion of the sentence. Replace with 'Investigators are encouraged to program atrial ATP 'ON' in all eligible patients with dual or triple chamber devices at their discretion.' Deletion of the sentence (technical correction).
9.1 Study procedures – Overview It is required that Atrial ATP is programmed 'ON' in at least 10 patients throughout the study, and CRT AutoAdapt in at least 5 patients.	Deletion of the sentence. Replace with 'Investigators are encouraged to program atrial ATP and/or CRT AutoAdapt 'ON' in all eligible patients at their discretion.'
9.3 / 9.4 / 9.5 /9.6 Program the following <u>optional</u> device settings: • For DR-T or HF-T QP patients with known history of atrial arrhythmia (except permanent AF): aATP 'ON'	Deletion of 'with known history of atrial arrhythmia (except permanent AF)'

This amendment is not substantial according to ISO 14155 section 5.6.4 e).

Coordinating Investigator

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Date	Signature

Senior Clinical Project Manager

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