

Audit Report

Internal Code: SM 001

Date of Report: 28 SEP 2008

Serbian Smoking Reduction / Cessation Trial (2SRT)

Investigator Site Audit

Dr. Draskovic, Belgrade, Serbia

Audit Report

for

Swedish Match AB

**118 85 Stockholm
Sweden**

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Type of Audit: Investigator Site Audit – Site 4

Auditor: Christiane Hartlieb-Wallthor-Sano, QA Consultant, Monheim
(Lead Auditor)

Sponsor: Swedish Match AB
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Sweden

Auditee: Dr. Silvela Draskovic
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Savska 23
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Place of Audit: Railway Health Institute, Savska 23, 11000 Belgrade, Serbia

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Report Reviewed by: Dr. Freddi Lewin
Date: **Date to be inserted**

Report Distributed to: Dr. Freddi Lewin
Swedish Match AB

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1 Executive Summary

At the request of Swedish Match AB Christiane Hartlieb-Wallthor-Sano conducted an investigator site audit pertaining to the clinical study "Serbian Smoking Reduction / Cessation Trial (2SRT) – SM 07-01". The audit took place at site # 4, i.e. Railway Health Institute in Belgrade, Serbia. Principal investigator is Dr. Silvela Draskovic. Christiane Hartlieb-Wallthor-Sano was accompanied by Dr. Biljana Radisavljevic, the responsible monitor of i3Research.

The most important findings outlined in this report were presented and discussed during the closing meeting on 10 SEP 2008 with the participants listed in [sections 4.3](#) of this report. The categorisation of significant findings is summarised below.

1.1 Objective and Extent of Audit

The objective of the investigator site audit was to assess the compliance with the trial protocol and the ICH Guideline for Good Clinical Practice and any other applicable reference documents.

1.2 Significant Findings

Critical *Findings, which affect the safety of the subjects, the reliability and integrity of the study data, are persistent violations of the protocol and/or regulations. (Urgent action recommended)*

- The quality of the study is compromised as follows:
 - No critical findings

Major *Findings that violate the protocol, GCP, Standard Operating Procedures (SOP's) and/or regulations but will not affect the acceptability of the study data.*

- The quality is compromised as follows:
 - Lack of evidence that patients have been adequately consented, i.e. informed consent document not personally dated by the patient
 - Failure to comply with the investigational plan, e.g. visits performed outside the time window, no early termination visit performed, unavailability of patient diary
 - Inadequate AE reporting
 - Failure to respond to the monitor's instructions (at monitoring visits and in follow-up letters)

Minor *Findings that require actions to improve the quality and/or efficiency of the systems used.*

- Minor findings are described in the report.

1.3 Conclusions

The investigator site audit revealed several major findings related to the conduct of the study as detailed above. Most of the issues had already been detected by the monitor and discussed with the investigator however corrective actions have not or only in part been implemented by the investigator.

The existence of the patients is not in doubt but the high rate of early terminators, i.e.

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patients withdrawing their informed consent, being lost-to-follow-up or terminating because of protocol violations, compromises the quality of the study. None of the patients has reached Week 24, the time for the evaluation of the primary endpoint.

All findings should be adequately addressed and the planned corrective actions in response to this audit report should be forwarded to and assessed by Swedish Match AB.

In summary, the investigator fails to conduct the clinical investigation according to the investigational plan even though the site has been re-trained on several occasions. Therefore it is recommended that the site does not continue to recruit any further patients.

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2 Introduction

At the request of Swedish Match AB Christiane Hartlieb-Wallthor-Sano conducted an investigator site audit pertaining to the clinical study "Serbian Smoking Reduction / Cessation Trial (2SRT) – SM 07-01". The audit took place at site # 4, i.e. Railway Health Institute in Belgrade, Serbia. Principal investigator is Dr. Silvela Draskovic. Christiane Hartlieb-Wallthor-Sano was accompanied by Dr. Biljana Radisavljevic, the responsible monitor of i3Research.

The objective of the investigator site audit was to assess the compliance with the trial protocol and the ICH Guideline for Good Clinical Practice and any other applicable reference documents.

3 Reference Documents

The audit was conducted against the following documents:

- ICH Topic E 6: Guideline for Good Clinical Practice, January 1997
- Clinical Study Protocol SM 07-01 Version 3 15 MAY 2007
- Information about Serbian Smoking Reduction / Cessation Trial (2SRT) 15 MAY 2007
- CRF Completion Guidelines Final Version 14 JAN 2008
- Final Monitoring Plan Version 2 FINAL 06 MAY 2008
- i3 Research Pre-Study Visit Report 05 JUN 2007
- i3 Research Monitoring Visit Reports 29 JAN 2007, 21 FEB 2008, 24 / 27 MAR 2008, 05 JUN 2008, 26 JUN / 07 JUL 2008, 07 AUG 2008

4 Scope of Audit

The audit was performed according to the audit plan dated 06 SEP 2008.

4.1 Opening Meeting

An opening meeting was held on 09 SEP 2008 with the following participants:

Dr. Silvela Draskovic	Principal Investigator
Vera Rakic	Study Nurse
Dr. Biljana Radisavljevic	Monitor, i3Research
Christiane Hartlieb-Wallthor-Sano	QA Consultant, Lead Auditor

During the opening meeting the purpose of the audit was described and the extent of the audit and the areas of interest were presented to the auditee. The documents to be made available for audit purposes were requested.

4.2 Audit

In preparation of the audit an agenda was prepared. The investigator site audit consisted of interviews of responsible personnel, review of documents and of the facilities including the storage area for the investigational product.

4.3 Closing Meeting

A short closing meeting was held on 10 SEP 2008 to present the major audit findings. The meeting lasted only appr. 25 minutes due to the late arrival of Dr. Draskovic and the

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subsequent time constraints.

Dr. Silvela Draskovic	Principal Investigator
Dr. Biljana Radisavljevic	Monitor, i3Research
Christiane Hartlieb-Wallthor-Sano	QA Consultant, Lead Auditor

The observations and findings are detailed in [section 5](#) of this report with recommendations for corrective actions.

4.4 Conclusion

The investigator site audit revealed several major findings related to the conduct of the study as detailed above. Most of the issues had already been detected by the monitor and discussed with the investigator however corrective actions have not or only in part been implemented by the investigator.

The existence of the patients is not in doubt but the high rate of early terminators, i.e. patients withdrawing their informed consent, being lost-to-follow-up or terminating because of protocol violations, compromises the quality of the study. None of the patients has reached Week 24, the time for the evaluation of the primary endpoint.

All findings should be adequately addressed and the planned corrective actions in response to this audit report should be forwarded to and assessed by Swedish Match AB.

In summary, the investigator fails to conduct the clinical investigation according to the investigational plan even though the site has been re-trained on several occasions. Therefore it is recommended that the site does not continue to recruit any further patients.

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5 Audit Result and Findings

5.1 Study Conduct, Resources, Facilities, Equipment

Introduction:

The study is performed at the Railway Health Institute in Belgrade, Serbia. All study supplies, i.e. CRF books, patients source documents, investigator site file, investigational product, laboratory supplies are stored in an office room where the patient visits also take place. The CRFs are kept in two lockable cupboards. The investigational product is stored in three refrigerators used only for storage purposes. The room is locked when not in use.

Patients are recruited from Railway employees and their families and by advertisements (posters placed in the Railway Health Institute). Subjects interested or responding to the advertisements are invited to the Institute. Dr. Draskovic informs them about the study and if willing to participate she obtains the informed consent and assesses their eligibility. Following the baseline examinations the patients are randomised using to the randomisation schedule provided.

So far very few AEs have occurred, one SAE occurred which was adequately reported.

Vera Rakic is the study nurse, she is only responsible for obtaining the blood samples and performing the spirometry. She was trained on how to perform the spirometry during the investigator meeting held in Belgrade. In addition she assists Dr. Draskovic with the maintenance of the study records and the investigator site file.

The site was initiated on 22 JAN 2008. The first subjects were enrolled on 25 JAN 2008. Up to now the site has enrolled 60 subjects out of which only 2 subjects (4213 and 4214) were ongoing at the time of this audit. 58 subjects were discontinued for various reasons, i.e. 21 subjects withdrew their informed consent, 22 subjects were lost to follow-up and 15 terminated early due to protocol violations, mainly because of non-adherence to the visit schedule.

Dr. Draskovic stated during the opening meeting that patients 4004 and 4047 have stopped smoking while being in the study.

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Summary Significant Findings: • N/A

Classification: critical major minor

Observation/Finding	Recommendation
For findings pertaining to the study conduct see section 5.5	

5.2 Investigator File

Introduction: The Investigator File review was not reviewed in detail.

The Identification Code List contains the names of 60 patients, the list was not checked for correctness and accuracy.

The monitoring visit log has been maintained and was signed by the monitor and auditor to document the audit.

Summary Significant Findings: • N/A

Classification: critical major minor

Observation/Finding	Recommendation
N/A	N/A

5.3 Informed Consents

Introduction: The patient information / informed consent version dated 15 MAY 2007 is the EC approved version and has been used for all 60 patients enrolled up to date. The informed consents are filed with the CRFs of each patient. 21 informed consents were selected at random and reviewed in more detail at this audit. The details are summarised in table **Overview Selected Informed Consents** attached to this audit report.

The patients have been informed by Dr. Draskovic about the study on the day of the baseline visit. A statement about the informed consent procedure can be found in the source documents as confirmed by random checks. All patients have signed the informed consent, patients 4001-4003, 4021, 4022, 4029-4050 and 4205-4214 also personally dated it. The other 23 patients (4004-4020, 4023-4028) did not personally date the informed consent document. The monitor noticed this during routine monitoring visits and re-trained the investigator with regard

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to an adequate informed consent procedure. In addition the monitor addressed the deviations in her follow-up letters. The monitor instructed Dr. Draskovic to add notes to the informed consent documents to confirm the date when the informed consent was obtained. The notes were added and signed by Dr. Draskovic however not yet by the patients.

Summary Significant Findings:

- Lack of evidence that patients have been adequately consented, i.e. informed consent document not personally dated by the patient

Classification: critical major minor

Observation/Finding	Recommendation
<p>23 patients have not dated their informed consent personally. Following the monitor's instructions the investigator added statements to confirm the date of informed consent however the patients' signatures are missing even though the patients may have returned to the site for study visits in the meantime. At the time of the audit all 23 patients have been discontinued, i.e. terminated early (withdrawal of informed consent, lost-to-follow-up, protocol violations).</p> <p>There are no notes in the source documents providing evidence of any attempts to obtain the patients' confirmation and signatures.</p>	<p>It is recommended to contact the patients urgently to obtain their confirmation. The attempts and the circumstances should be adequately documented.</p> <p>In case this is not possible, e.g. patients who have withdrawn their informed consent, the reasons should be well documented in the patients' source documents.</p>
<p>Patient 4213 signed the informed consent and wrote 26 APR 2008 as date. According to the source notes the patient was consented on 24 JUN 2008. The mistake has already been corrected on the informed consent document however the patient's signature to confirm the correction is still pending.</p>	<p>It is recommended to obtain the patient's signature as soon as possible.</p>

5.4 Product Accountability

Introduction: The site received several shipments of investigational product, i.e. starter kits and logs (sachets of 0,5 g and 1 g, liquorice and eucalyptus). The investigational product is stored in 3 refrigerators placed in the study examination room. The temperature is controlled on a regular basis (every three days) and has always been within the required range.

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The patients have been randomised using the randomisation schedule provided except for patient 4012 who was incorrectly randomised and received the wrong logs. Due to this deviation the patient was withdrawn as per sponsor decision.

Accountability was performed for the starter kits. The site has been provided with a total of 110 starter kits, 60 have been used for the patients enrolled so far, 48 are available at the site. 2 starter kits (#4230 and #4231) have been retrieved by Bozidar Jablan on 09 SEP 2008 for the sponsor for re-test purposes. The overall accountability of the starter kits is correct, accountability of the logs has not been performed.

The dispensing is documented on a dispensing log which was not reviewed in detail except for the entries for patients 4004, 4024 and 4047. The entries are correct and reflect the information provided in the CRFs of these patients.

Summary Significant Findings: • N/A

Classification: critical major minor

Observation/Finding	Recommendation
Bozidar Jablan retrieved kits # 4230 and # 4231 on 09 SEP 2008 for the sponsor. The collection has not been documented.	The collection of kits # 4230 and # 4231 by Bozidar Jablan on 09 SEP 2008 should be documented on the respective form and confirmed by the site by their dated signature.
A tear off label attached to the starter kits with details about the investigational product is placed onto the top copy of the respective CRF page. During monitoring visits the top copy is collected, details regarding the investigational product are added in handwriting.	It is recommended to file xerox copies of the CRF pages at the site.

5.5 CRF Review and Source Data Verification

Introduction:

As per 10 SEP 2008 the site has enrolled and randomised 60 patients. During the audit the medical charts of patients 4004, 4024 and 4047 selected at random were reviewed in detail and 100 % source data verified. The diary of patient 4205 was reviewed and the AE reporting was reviewed for patient 4010. In addition the source documents of all other patients were reviewed in terms of availability and checked with regard to the patients' final status and the reasons for

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early termination.

Patient specific findings are listed per patient, the general findings are summarised under General Observations / Findings.

General Observations/Findings

- Summary Significant Findings:**
- Failure to comply with the investigational plan, e.g. visits performed outside the time window, no early termination visit performed, unavailability of patient diary
 - Inadequate AE reporting
 - Failure to respond to the monitor's instructions (at monitoring visits and in follow-up letters)

Classification: critical major minor

Observation/Finding	Recommendation
The source documents are kept in a plastic sleeve filed in the patients' CRF books. For source documents, e.g. patients 4004, 4024, 4047, more than one piece of paper has been used however the patient's name is only recorded on the first page.	The investigator should be asked to record the patient's name on each document / piece of paper.
Except for patient 4025 the patients have not returned the diaries.	The investigator should be instructed to make every effort to obtain the patient diaries. Upon receipt they should be carefully reviewed, omissions or discrepancies should be corrected, if possible, and/or explained. The status of the diaries, e.g. returned / not returned should be noted in the patients' source documents in addition to the attempts to obtain them.
Study related visits have in part been performed late and outside the protocol allowed time window. The sponsor regarded them as being protocol violations and decided that the patients prematurely terminate the study. 14 patients have been withdrawn due to protocol violations. In the source notes there were no explanations provided, e.g. why the visits were delayed. Early termination visits have not been performed yet.	The investigator should be asked to document the reason for the late visits and that per sponsor decision the patient was withdrawn. A note should also be added how the patient has been informed about the decision. The early termination visits should be scheduled / performed as soon as possible. Any subsequent entries should be clearly marked as such and confirmed by dated signature.
22 patients have been classified as lost-to-follow-up. There is not always a record in the	The site should be instructed to perform three attempts prior to declaring a patient

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Observation/Finding	Recommendation
patients' source documents stating this. In addition not for all patients three attempts have been made to contact the patient, e.g. 4011, 4020, 4046 or 4049. In cases where three attempts were made they were not always done in a timely manner, e.g. patient 4037 1 st 20May08, 2 nd 15Jun08 and 3 rd 20Aug08.	lost-to-follow-up. The three attempts should be performed in a reasonable time interval, e.g. 1 month. A statement should be added to the patients' source documents explaining the number of attempts and the time intervals. The date of the last attempt may then be used as the date for the final status requested in the CRF.
Patients 4042 and 4044 were lost to follow-up 1 and 2 weeks respectively after their baseline visit. Patient 4042 went on a business trip for 6 months, the reason for patient 4044 is not known.	The investigator should be instructed to carefully select patients and to inquire whether the patients are willing and able to follow the visit schedule required by the protocol.
Out of 60 patients 21 withdrew their informed consent. It is unclear why such a high number of patients did not want to continue even though many of them did have a benefit, i.e. a reduction in the number of cigarettes smoked per day by replacing cigarettes by Snus, e.g. patient 4016. For most of the patients no reason is provided in the source notes. A few patients withdrew their informed consent because they wished to continue smoking, e.g. 4024, 4025 and 4030. The investigator contacted the patients to schedule an early termination visit.	The investigator should be instructed that study related procedures may not be performed in patients who have withdrawn their informed consent. The date of withdrawal should be clearly stated in the patients source documents and a reason should be provided if the patient is willing to provide one.
Dr. Biljana Radisavljevic, the responsible monitor of i3Research, noticed many of the deficiencies at her routine monitoring visits and discussed them with the investigator. In addition she summarised the findings in her follow-up letters however the investigator did not fully respond to these.	The investigator should be re-trained with regard to GCP and the investigator's responsibilities in a clinical trial.

Patient: **4004** (not part of the CRFs selected by the monitor for SDV)

Section: **Source Data and CRF Completion**

Summary Significant Findings:

- Inadequate AE reporting
- Failure to comply with the investigational plan, e.g. no early termination visit performed, unavailability of patient diary

Classification: critical major minor

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Observation/Finding	Recommendation
The patient had her week 12 visit on 21 APR 2008. Due to a cold the laboratory sample was not taken on that day but postponed to a later day. The "cold" was not recorded as an AE in the CRF.	"Cold" should be recorded as an AE in the CRF.
The patient is 43 years of age. No information could be found in source whether or not the patient is pregnant or lactating.	It is recommended to add information on the patient's status, if available. The addition should be clearly marked as a subsequent entry and signed and dated by the PI.
No information could be found in source that the patient discontinued the study and the reason for discontinuation.	It is recommended to add this information, as available. The addition should be clearly marked as a subsequent entry and signed and dated by the PI.
According to the source no early termination visit as required by the protocol has been performed.	It is recommended to perform the early termination visit as soon as possible and provide an explanation for the delay.
According to the source documentation the patient has not yet returned the patient diary.	It is recommended to request the patient diary as soon as possible. Upon receipt the information provided by the patient should be carefully reviewed. Omissions should be discussed with the patient, corrections should be made as appropriate.
Laboratory results out of range have not all been assessed. The <u>original</u> laboratory reports are signed but not dated.	It is recommended that the investigator signs and dates the fax copy of the laboratory report and assesses all out of range results. Once the original report is received the investigator should again assess the out-of-range results and sign and date the report.
According to the patient's source documents the laboratory results of the blood sample taken on 29 JAN 2008 was received on 30 JAN 2008. The laboratory report however was signed with the date of 29 JAN 2008.	The discrepancy in dates should be clarified and corrected / explained as appropriate.
The source states that at visit 2 investigational product was taken from bin 2 however 2 logs were taken from bin 5 as evidenced from other documents.	The discrepancy should be corrected in the source document as appropriate.
There are no source notes for spirometry, CO and vitals for week 12.	The source should be amended as appropriate. The additional entry should be clearly marked as such and confirmed by the investigator's dated signature.

Patient: 4024 (not part of the CRFs selected by the monitor for SDV)

Section: Source Data and CRF Completion

Summary Significant Findings: • N/A

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Classification: critical major minor

Observation/Finding	Recommendation
Laboratory reports have been signed but not dated, e.g. baseline.	<p>It is recommended that the investigator adds a statement when the results have been reviewed, if known.</p> <p>It is recommended that the investigator reviews all laboratory reports to ensure that they are all signed and dated and that all out-of-range results are assessed.</p>

Patient: **4047** (not part of the CRFs selected by the monitor for SDV)

Section: **Source Data and CRF Completion**

Summary Significant Findings: • Incomplete source documentation

Classification: critical major minor

Observation/Finding	Recommendation
There are no source notes for spirometry, CO and vitals for Week 2 performed on 01 APR 2008.	The source should be amended as appropriate. The additional entry should be clearly marked as such and confirmed by the investigator's dated signature.
Laboratory reports have been signed but not dated, e.g. baseline and week 12, and out of range results have not been assessed on the lab report, e.g. fibrinogen at week 12.	It is recommended that the investigator assesses all out of range results on the lab reports and adds a statement when the results have been reviewed, if known.

Patient: **4010** (not part of the CRFs selected by the monitor for SDV)

Section: **Source Data and CRF Completion**

Summary Significant Findings: • Inadequate AE reporting

Classification: critical major minor

Observation/Finding	Recommendation
At Week 12 visit the patient reported a cold. The "cold" was not recorded as an AE in the CRF.	<p>"Cold" should be recorded as an AE in the CRF.</p> <p>It is recommended that the investigator reviews the source documents of all patients</p>

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Observation/Finding	Recommendation
	to ensure that all AE are adequately recorded and reported.

Patient: 4205

Section: Source Data and CRF Completion

Summary Significant Findings: N/A

Classification: critical major minor

Observation/Finding	Recommendation
The patient returned the diary however dates have not been completed.	It is recommended to discuss possibilities to obtain the missing data with the investigator.