Resminostat:
A Novel Oral Histone Deacetylase Inhibitor in Phase II Clinical Development
Dr. Bernd Hentsch, Chief Development Officer, 4SC AG, Germany
This presentation may contain projections or estimates relating to plans and objectives relating to our future operations, products, or services; future financial results; or assumptions underlying or relating to any such statements; each of which constitutes a forward-looking statement subject to risks and uncertainties, many of which are beyond our control. Actual results could differ materially, depending on a number of factors.
### 4SC AT A GLANCE

<table>
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<tr>
<th>MISSION</th>
<th>4SC develops targeted small-molecule therapies against inflammation &amp; cancer</th>
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<tr>
<td>BUSINESS FOCUS</td>
<td>Broad &amp; maturing product pipeline – multiple clinical trials in Phase I and II</td>
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<td>Integrated drug discovery and development platform</td>
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<td>Licensing agreements with biopharmaceutical companies</td>
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<td>FINANCE &amp; SHARES</td>
<td>Committed investor base &amp; sufficient cash reserves to reach value inflection points</td>
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<td>Listed on Frankfurt Stock Exchange</td>
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<td>(Prime Standard: VSC)</td>
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<tr>
<td>ATTRACTIVE GOALS AHEAD</td>
<td>Lead inflammation product: <em>Vidofludimus</em></td>
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<tr>
<td></td>
<td>• Phase IIb study in IBD in preparation</td>
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<td></td>
<td>Lead oncology product: <em>Resminostat</em></td>
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<td>• Pivotal phase III programme in oncology in preparation</td>
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### AUTOIMMUNE DISEASES

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Mode</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Vidofludimus</td>
<td>Rheumatoid Arthritis (RA)</td>
<td>Inhibition of DHODH and IL-17 signaling</td>
<td>COMPONENT</td>
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<td>(4SC-101)</td>
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<tr>
<td>Vidofludimus</td>
<td>Inflammatory Bowel Disease (IBD)</td>
<td>Inhibition of DHODH and IL-17 signaling</td>
<td>ENTRANCE</td>
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<td>(4SC-101)</td>
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### ONCOLOGY

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<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Mode</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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</thead>
<tbody>
<tr>
<td>Resminostat*</td>
<td>Hepatocellular Carcinoma (HCC)</td>
<td>Oral Pan Histone-Deacetylase (HDAC)-Inhibitor</td>
<td>SHELTER</td>
<td></td>
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<td>(4SC-201)</td>
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<tr>
<td>Resminostat</td>
<td>Hodgkin’s Lymphoma (HL)</td>
<td>Oral Pan Histone-Deacetylase (HDAC)-Inhibitor</td>
<td>SAPHIRE</td>
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<tr>
<td>Resminostat*</td>
<td>K-ras mut. Colorectal Cancer (CL)</td>
<td>Oral Pan Histone-Deacetylase (HDAC)-Inhibitor</td>
<td>SHORE</td>
<td></td>
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<tr>
<td>(4SC-201)</td>
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<tr>
<td>4SC-203</td>
<td>Oncology</td>
<td>Multi kinase inhibition – selective of FLT3 and VEGF-R2</td>
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<tr>
<td>4SC-205</td>
<td>Solid Tumours and Lymphoma</td>
<td>Oral Eg5 Kinesin inhibitor</td>
<td>AEGIS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4SC-202</td>
<td>Haematologic and Solid Tumours</td>
<td>Oral selective HDAC inhibitor with strong anti-mitotic effect</td>
<td>TOPAS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4SC-207</td>
<td>Haematologic and Solid Tumours</td>
<td>Oral resistance breaking cell cycle blocker</td>
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* Cooperation with Yakult Honsha, Japan
RESMINOSTAT

4SC in $192M Agreement for Japan Rights to Resminostat

By Cormac Sheridan
BioWorld Today Correspondent

Setting down a weighty marker for partnering deals elsewhere, 4SC AG is pocketing €6 million (US$8.7 million) up front and could earn another €127 million in milestones, for licensing Japanese rights to its oral pan-histone deacetylase (HDAC) inhibitor resminostat (4SC-201).

Tokyo-based Yakult Honsha Co. Ltd. gained exclusive rights to develop and commercialize the compound in all oncology indications in its home country.

It will focus initially on hepatocellular carcinoma (HCC), which has a relatively high prevalence in Asian populations, and on patients with colorectal carcinoma (CRC) who harbor KRAS mutations.

The Martinsried, Germany-based company is pursuing an aggressive development strategy, CEO Ulrich Dauer told BioWorld Today.
**RESMINOSTAT: CLINICAL DEVELOPMENT STRATEGY**

**ENTRY INTO HEMATOLOGICAL INDICATIONS**

Hodgkin’s Lymphoma “SAPHIRE” (completed)

- Relapsed/refractory HL patients who are resistant to 2nd line therapy have very low survival rate
- 3rd line treatment
- Single-arm study
- Simon 2-stage design
- Resminostat monotherapy
- Aiming for short development timeline and fast market entry

**FIRST ENTRY INTO SOLID TUMOR INDICATIONS**

Hepatocellular Carcinoma “SHELTER” (on-going)

- Only one therapy available in advanced HCC (sorafenib)
- Very high unmet need in Asia-Pacific region
- 2nd line therapy
- 2-arm study
  - Resminostat monotherapy
  - Resminostat + sorafenib combination therapy

**EXTENDED ENTRY INTO SOLID TUMOR INDICATIONS**

Colorectal Cancer “SHORE” (on-going)

- 3rd most frequent cancer
- Ph. I/II with patients w/ KRAS-mutated tumors
- 2nd line therapy
- Randomized, 2-arm study
  - FOLFIRI (standard chemo regimen) +/- resminostat combination therapy

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**RESMINOSTAT IS EXPLORED AS SINGLE AGENT ANTI-CANCER DRUG AND AS A (RE-)SENSITIZING AGENT IN COMBINATION WITH ESTABLISHED TUMOR THERAPIES.**

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7-8 December 2011  World Epigenetics Summit, Munich
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MONOTHERAPY APPROACH:
PHASE II IN HODGKIN’S LYMPHOMA (HL)
Relapsed and/or refractory HL patients who are resistant to 2\textsuperscript{nd} line treatment have 5-year overall survival rate of only 17\%\textsuperscript{1}

- High medical need for new 3\textsuperscript{rd} line options with less long-term toxicity\textsuperscript{2}
- Regulatory agencies open to small pivotal trial(s), allowing for rapid development and near-term launch

1\textsuperscript{st} and 2\textsuperscript{nd} line therapies are efficacious, but patients frequently develop secondary malignancies later in life induced by heavy exposure to chemotherapy

- High medical need for reduction of chemo during earlier lines of treatment

Orphan drug status granted in USA and EU

RESMINOSTAT IN HL THERAPY:

1. ESTABLISHING RESMINOSTAT AS NEW THIRD-LINE OPTION

2. EXTENSION OF RESMINOSTAT TO EARLIER LINES OF TREATMENT, E.G., MAINTENANCE THERAPY APPROACH POST CHEMO / RADIATION / ASCT

\textsuperscript{1} Sirohi \textit{et al.}, \textit{Ann. Oncol.} 2008; 19(7):1312-9
\textsuperscript{2} Datamonitor, Pipeline Insight: \textit{Lymphomas, Multiple Myelomas and Myelodysplastic Syndromes} (2010)
THE SAPHIRE TRIAL: RESMINOSTAT IN HL

- Phase II open-label, single-arm, multi-center, multinational trial

- Once-daily oral dosing of resminostat (600 mg and 800 mg); Simon two-stage design; 14-day treatment cycles (“5+9”, i.e. 5 days on, 9 days off)

- 12 weeks of therapy during main treatment phase; optional treatment extension thereafter upon demonstration of clinical benefit

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>MAIN TREATMENT</th>
<th>FOLLOW-UP PHASE</th>
<th>END POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory HL patients</td>
<td>Monotherapy</td>
<td>For patients with response/stable disease</td>
<td>ORR</td>
</tr>
<tr>
<td>Relapsed HL patients</td>
<td>600 mg or 800 mg resminostat</td>
<td>Up to 12 months</td>
<td>OS, PFS, TTP, DOR</td>
</tr>
<tr>
<td></td>
<td>34 patients</td>
<td></td>
<td>Safety, PK, Biomarkers</td>
</tr>
</tbody>
</table>

1 www.clinicaltrials.gov: NCT01037478
SAPHIRE STUDY: CASE REPORT

PET/CT Image at Level 1

Min: 0.5 SUV
Max: 16.1 SUV
Mean: 3.8 SUV
StdDev: 4.0 SUV

Min: 0.4 SUV
Max: 9.6 SUV
Mean: 2.3 SUV
StdDev: 2.9 SUV

Min: 0.3 SUV
Max: 3.3 SUV
Mean: 1.2 SUV
StdDev: 0.9 SUV

Min: 0.3 SUV
Max: 3.3 SUV
Mean: 1.2 SUV
StdDev: 0.9 SUV

PET/CT Image at Level 2

Min: 0.4 SUV
Max: 14.9 SUV
Mean: 3.6 SUV
StdDev: 3.4 SUV

Min: 0.2 SUV
Max: 11.6 SUV
Mean: 4.5 SUV
StdDev: 2.7 SUV

Min: 0.4 SUV
Max: 7.6 SUV
Mean: 2.9 SUV
StdDev: 1.9 SUV

Min: 0.2 SUV
Max: 7.7 SUV
Mean: 1.8 SUV
StdDev: 1.5 SUV

PET Image

Level 2

Baseline

6 Weeks

12 Weeks

20 Weeks

Level 1
SAPHIRE: PRIMARY ENDPOINT ACHIEVED

19 PATIENTS (55.9%) WITH CLINICAL BENEFIT;
12 PATIENTS (35.3%) QUALIFIED AS RESPONDERS.

* Clinical activity was measured through PET/CT, *i.e.*, combination of positron-emission tomography (PET) and computer tomography (CT). Complete and partial responses were measured according to Cheson criteria, and metabolic responses according to EORTC criteria.

DCR = Disease Control Rate | ORR = Overall Response Rate

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Advanced data will be presented at the Annual Meeting of the American Society of Hematology (ASH), San Diego, 10-13 December 2011:
Session 623: Lymphoma - Chemotherapy, December 11
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THE PRINCIPLE OF (RE-)SENSITIZATION OF DRUG TOLERANT CANCER CELLS
Growing evidence indicates that resistance to cancer drugs involves a reversible “drug-tolerant” state, and that HDACs play crucial role in drug tolerance development\(^1\)

<table>
<thead>
<tr>
<th>Sensitive</th>
<th>Tolerant</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Majority of cancer cells at earlier stages of disease or that are treatment-naïve are sensitive to drugs</td>
<td>- Histone deacetylases promote epigenetic modifications that lead to “Cancer Stem Cell” like characteristics, and reversible tolerance of even high-dose drug treatment</td>
<td>- Genetic alterations due to accumulation of mutations lead to stable and irreversible drug resistance by various mechanisms, e.g., drug target mutations, drug pathway mutations, enhanced drug efflux</td>
</tr>
<tr>
<td>- Such cells are accessible for therapy with chemo and targeted agents</td>
<td>- Combining therapies with HDAC inhibitors could shift drug tolerant cells back into drug sensitive state =&gt; “(re-)sensitization”</td>
<td></td>
</tr>
</tbody>
</table>

- Early application of HDAC inhibitors could prevent formation of drug tolerance

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1 \(Sharma \textit{et al.}, \textit{Cell}, 2010\)

**HDACs PROMOTE REVERSIBLE DRUG TOLERANCE THROUGH EPIGENETIC MODIFICATION**

The potential ability to prevent and reverse drug tolerance explains the suitability of HDAC inhibitors as promising combination agents.
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MONOTHERAPY & (RE-)SENSITIZATION:
PHASE II IN HEPATOCELLULAR CARCINOMA
HEPATOCELLULAR CARCINOMA (HCC) IS LACKING EFFECTIVE TREATMENT OPTIONS

- High unmet medical need due to limited treatment options
  - Prognosis of patients with unresectable HCC is poor, with median survival of less than 1 year\(^1\) and ca. 700,000 deaths/year worldwide\(^2\)
  - Sorafenib is the only approved 1\(^{st}\) line therapy for advanced-stage HCC; no 2\(^{nd}\) line therapy available after progression on sorafenib
  - High medical need to improve 1\(^{st}\) line options, and urgent need for 2\(^{nd}\) line options with focus on re-sensitization of sorafenib-refractory tumors

<table>
<thead>
<tr>
<th>Liver Stage</th>
<th>Treatment intervention</th>
<th>1(^{st}) line systemic regimens used</th>
<th>2(^{nd}) line regimens used</th>
</tr>
</thead>
</table>
| Resectable  
  BCLC 0,A: 30%-40%           | • Surgery  
                        | • NA                                    | • NA                         |
| Unresectable/metastatic  
  BCLC B: 20%  
  BCLC C: 40%  
  BCLC D: 10%       | • Chemoembolization (B)  
                        | • Sorafenib OS: 10.7 months  
                        | • Exploratory drugs  
                        | • Sorafenib TTP: 5.5 months  
                        | • Best supportive care  
                        | • Placebo TTP: 2.8 months  
                        | • OS: 3 to 6 months  
                        | • TTP: ~ 1.5 months  

In HCC patients, high HDAC-1 expression correlates with:

- Higher incidence of cancer cell invasion into the portal vein
- Poorer histological differentiation
- More advanced TNM stage
- Lower survival rates after surgical resection

Furthermore, expression levels of HDAC-1, -2 and -3 correlate with HCC recurrence rate following liver transplantation

Resminostat acts synergistically in combination with sorafenib

Orphan drug status for resminostat in HCC granted in USA and EU

HIGH LEVELS OF HDAC EXPRESSION ARE LINKED TO POOR PROGNOSIS IN HCC.

1 Rikimaru et al., Oncology 2007; 72:69-74
2 Wu et al., PLoS One 2010; 5:e14460
RESMINOSTAT: THE PHASE II SHELTER TRIAL IN HCC

- Ph. II open-label, two-arm, multi-center trial in Germany and Italy
- Once-daily oral dosing of resminostat; 14-day treatment cycles ("5+9", i.e., 5 days on, 9 days off; continuous administration of sorafenib)
- 12 weeks of therapy during main treatment phase; optional treatment extension thereafter upon demonstration of clinical benefit

**INCLUSION CRITERIA**
- Sorafenib refractory HCC patients
- Advanced HCC

**COMBINATION**
- Sorafenib+Resminostat dose escalation incl. approx. 18 patients
- Sorafenib+Resminostat at MTD 15 patients

**MONOTHERAPY**
- 600 mg Resminostat
- 15 patients

**END POINTS**
- PFS
- TTP, RR, OS
- Biomarkers, Safety, PK

**OPTIONAL EXTENSION**
- 10 patients

**END POINTS**
- PFS
- TTP, RR, OS
- Biomarkers, Safety, PK

**OPTIONAL EXTENSION**
- 10 patients

1 www.clinicaltrials.gov: NCT00943449
Interim Progression Free Survival Rate (PFSR, n=18):¹
- After 6 weeks (Cycle 3): 61% (11/18)
- After 12 weeks (Cycle 6): 50% (8/16)

Resminostat and sorafenib can be combined in advanced HCC patients

New therapy opportunity for 1st and 2nd line development

INTERIM PFSR* (PROGRESSION FREE SURVIVAL RATE):
AT 6 WEEKS (CYCLE 3) = 61% (11/18) / AT WEEK 12 (CYCLE 6) = 50% (8/16)

¹ Data represent the total patient population from both study arms, i.e. monotherapy and combination (dose escalation and maintenance). See www.4sc.de/product-pipeline/publications-posters
:: BY PEOPLE. WITH PEOPLE. FOR PEOPLE

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CLINICAL SAFETY SUMMARY
Profile of Adverse Events\(^1\)

- GI disturbances (nausea, vomiting) and fatigue (esp. in long-term treatment)
- Hematological effects (thrombocytopenia, anemia) → predominant in SAPHIRE
- Mild to moderate in most cases; manageable, generally not treatment-limiting
- Cardiovascular effects typical of other HDAC inhibitors were not prominent (analysed via central ECG assessments)

Profile of Serious Adverse Events\(^1\)

- Heterogeneous; mostly related to the underlying advanced disease stages
- In the majority, hematological events (thrombocytopenia, anemia) in SAPHIRE; causal relationship to the heavily pretreated HL population; manageable and only in rare cases treatment-limiting

RESMINOSTAT’S FAVORABLE SAFETY PROFILE RENDERS IT A COMBINATION PARTNER FOR VARIOUS CANCER THERAPIES, INCL. CYTOTOXICS AND NOVEL TARGETED THERAPIES IN SOLID AND HEMATOLOGICAL TUMORS.

\(^1\) Phase I, SHELTER, SAPHIRE, and SHORE trials
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PHASE I/II IN COLORECTAL CANCER (CRC)
Colorectal carcinoma (CRC) is third most common cancer (~1.2M cases worldwide in 2008) and fourth leading cause of cancer-related mortality (~600,000 deaths in 2008)\(^1\)

Epidermal growth factor receptor (EGFR) inhibitors have expanded CRC treatment options, *e.g.*, cetuximab and panitumumab

Substantial evidence now exists that KRAS mutations, which are present in approx. 35%-45% of CRC patients, are associated with insufficient response to EGFR targeting therapies\(^2\)

Patients with CRC harboring KRAS mutations with high medical need for additional therapy options

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Class I HDACs found to be highly expressed in colorectal adeno-carcinomas

HDAC-3 is overexpressed in ~50% of all colon adeno-carcinomas

HDAC-2 is upregulated in APC-mutant cells and in most colon cancers, and confers survival advantage to colon tumor cells

Patients showing overexpression of class I HDAC isoforms had dramatically reduced survival times

Kaplan-Meier survival curves dependent on HDAC isoform expression patterns. Overall survival dependent on HDAC-1 (A), HDAC-2 (B), HDAC-3 (C), and combined HDAC (D) expression. P values were calculated with log-rank test.

HDAC EXPRESSION CORRELATES WITH POOR PROGNOSIS IN CRC PATIENTS.

**RESMINOSTAT: PHASE I/II “SHORE” TRIAL IN CRC**

- Ph. I/II trial recruiting up to 70 patients
  - Randomized, open-label, multi-center, 2-arm study in combination with FOLFIRI vs. FOLFIRI alone in 2nd line therapy
  - Once-daily oral dosing of *resminostat* at MTD (determined through dose escalation arm in 20 patients) with FOLFIRI; “5+9” treatment cycles until progression

**INCLUSION CRITERIA**
- Colorectal cancer
- KRAS-mutated
- Prior 5-FU therapy
- No previous *irinotecan*

**COMBINATION**
- FOLFIRI + resminostat
- 25 patients

**FOLFIRI CONTROL**
- FOLFIRI alone
- 25 patients

**END POINTS**
- PFS
- TTP, RR, DOR, OS
- Biomarkers, Safety, PK

1 [www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT001277406
[www.4sc.de/product-pipeline/publications-posters: 22nd EORTC-NCI-AACR Symposium, Berlin, 2010](http://www.4sc.de/product-pipeline/publications-posters)
SHORE Study Status

- First dose levels completed
- Dose escalation ongoing

Resminostat is administered prior to, during and after FOLFIRI dosage

Treatment duration (number of cycles) is not limited
- Treatment up to progression, toxicity or withdrawal of consent
Clinical development program in 3 indications ongoing:

**HL**
- Low survival rate among relapsed/refractory HL patients resistant to 2nd line therapy
- Clear, objective responses to resminostat monotherapy in heavily pretreated patients
- Target lesion size reductions of >50%; frequent decreases in metabolic tumor activity
- Excellent safety profile in heavily pretreated patient population

**HCC**
- Only single therapy line available, i.e. sorafenib
- Interim data show frequently 3 months PFS reached
- Very good safety profile in severely debilitated patients
- Large commercial potential in Asia-Pacific, incl. China
- Novel mode of action of “(Re-)Sensitization” in this solid tumor; preclinical synergism with sorafenib

**CRC**
- CRC patients with KRAS-mutant tumors have limited treatment options
- Extension to KRAS-wild type patients possible
- Combination may be expandable to 1st line
- Combination with cytotoxics suitable for other cancers
- “(Re-)Sensitization” approach, strong preclinical activity with irinotecan
ACKNOWLEDGEMENT

THANKS TO THE PATIENTS AND THEIR FAMILIES

THANKS TO THE CLINICAL INVESTIGATORS AND STUDY GROUPS
THANK YOU VERY MUCH!

:: CONTACT
Dr. Bernd Hentsch, CDO
bernd.hentsch@4sc.com
Tel: +49 (0) 89 700 763 0

www.4sc.com