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| **Name of Sponsor/Company:**<br><br>GMIHO – Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH<br>Alte Jakobstraße 77<br>10179 Berlin | Individual study table referring to part of the dossier<br><br>not applicable | |
| **Name of Finished Product:**<br><br>Glivec® | Volume | |
| **Name of Active Ingredient:**<br><br>Imatinib (STI571) | Page | |

**Title of Study:**

CRESCENDO (Compliance: Role Emerges for Success in CML: Evaluation aND Optimisation):
A prospective, multi-center, phase IV study to assess the compliance in patients with Philadelphia chromosome-positive (Ph+) and/or BCR-ABL positive chronic myelogenous leukaemia (CML) under long-term imatinib therapy

**Investigators:**

[redacted]

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IFS - Interdisziplinäres Facharztzentrum Sachsenhausen, Fachärzte für Innere Medizin, Gastroenterologie, Onkologie, Hämatologie, Stresemannallee 3, 605[redacted] Frankfurt

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|---|---|
| MVZ im Medico, Husener Str. 48, 330[redacted] Paderborn | |
| **Previous related Publications (reference):**<br><br>**na** | |
| **Studied period (years): 3**<br><br>**Date of first enrolment** 15.12.2010<br><br>**Date of last completed** 03.06.2013 | **Phase of development:**<br><br>IV |

**Objectives:**

Primary objective:
To assess patient's compliance before and after intervention by comparison of the number of imatinib (Glivec®) tablets taken before and after intervention.

Secondary objectives:

- to correlate the compliance assessed by pill count (conventional pill count and pill count using SmartBlister® in 50 patients) with the results obtained by the questionnaires and interviews
- to monitor the efficacy of imatinib as assessed by PCR testing (BCR-ABL load, % IS)
- to correlate the compliance with the efficacy as assessed by PCR testing
- to correlate the compliance with imatinib blood levels during imatinib treatment

**Methodology:**

A prospective, multi-center, open-label, Phase IV study in patients with Ph+ and/or BCR-ABL+ CML in chronic phase who require treatment with imatinib. Patients were treated for a total of 12 months, 6 months without and 6 months with compliance supporting measures (to be chosen by the patients between an information service "*Leben mit CML*" or the use of a daily diary). The study did also utilize questionnaires and patient-interviews for assessing compliance as well as blood plasma level measurements and routine CML monitoring measures (PCR and hematology) for assessing efficacy of CML treatment. The outcome of compliance and treatment efficacy was correlated. After the baseline visit (Day 1 of month 1) four subsequent visits with a three-months interval have been conducted (Visit 2-5 at months 3, 6, 9 and 12, respectively).

**Number of Patients (planned and analysed):**

Planned: 200 Analysed: 104 (included)

118 patients signed the informed consent and were screened for participation in the trial.
4 patients did not fulfil all in- and exclusion criteria or had no further study documentation and 8 patients did not participate in the planned intervention and are only listed for Safety (Table 1).

10 patients prematurely ended the study (Table 2). 5 patients out of the 8 who did not choose an intervention, 4 out of the 64 who choose the information service (IS-group) and 1 out of the 35 who choose the daily diary intervention (DD-group). The reasons for discontinuation are given in Table 3.

**Table 1**: List of patients not included in the analysis

| Patient number | Date of Informed Consent | End of Study | Reason for exclusion |
|---|---|---|---|
| 0030003 | 30MAR2011 | 21SEP2011 | Premature withdrawal |
| 0070002 | 19JAN2011 | 11FEB2011 | no study documentation |
| 0070004 | 19JAN2011 | 27APR2011 | no study documentation |
| 0070016 | 16MAR2011 | 25JUL2011 | no study documentation |
| 0090004 | 09JUN2011 | 31MAY2012 | No participation in Intervention program |
| 0100001 | 20APR2011 | 20APR2011 | Withdrawal of consent |
| 0110005 | 29APR2011 | 08JUN2012 | No participation in Intervention program |
| 0110012 | 15JUN2011 | 13NOV2011 | No participation in Intervention program |
| 0110019 | 21JUL2011 | 21AUG2012 | No participation in Intervention program |
| 0110020 | 22NOV2011 | 02MAR2012 | no study documentation |
| 0170001 | 28MAR2011 | 20JUN2011 | No participation in Intervention program |
| 0220010 | 08MAR2012 | 12JUN2012 | screening failure |

**Table 2:** Patients disposition

| No. of patients | No intervention N=8 | IS - group N=64 | DD - group N=35 | IS -& DD-group N=7 | Overall N=104 |
|---|---|---|---|---|---|
| signing Informed Consent | | | | | 118 |
| without documentation | | | | | 4 |
| included in the study | 8 | 64 | 35 | 7 | 114 |
| who completed the study | 3 | 60 | 34 | 7 | 104 |
| who discontinued prematurely | 5 | 4 | 1 | 0 | 10 |

**Table 3:** Patients who discontinued prematurely

| Patient number | Reason | Relevant information | Date of first study medication | Date of Dis-continuation |
|---|---|---|---|---|
| **No study specific intervention** | | | | |
| 0030003 | Adverse event(s) | - | 30MAR2011 | 21SEP2011 |
| 0100001 | Subject withdrew consent | - | 20APR2011 | 20APR2011 |
| 0110012 | Death | - | | 13NOV2011 |
| 0170001 | Subject withdrew consent | No further investigations done in the trial | 28MAR2011 | 20JUN2011 |
| 0220010 | Abnormal test procedure result(s) | No MMR because BCR-ABL 0.16% -> screening failure | 08MAR2012 | 12JUN2012 |
| **Intervention: Information service group** | | | | |
| 0070018 | Administrative problems | After downfall patient will be subserved by special - care | 12JUL2011 | 18JAN2012 |

| | | | | |
|---|---|---|---|---|
| | | home, patient will not came to our site any longer | | |
| 0090013 | Administrative problems | Pat. moved in another city, without another contact at site on sep-2012 | 26JAN2012 | 30SEP2012 |
| 0110014 | Subject withdrew consent | | 21JUN2011 | 27APR2012 |
| 0190005 | Administrative problems | Change to nilotinib because of patients request | 16APR2012 | 21MAR2013 |
| **Intervention: Daily diary group** | | | | |
| 0030001 | Adverse event(s) | | 02FEB2011 | 19DEC2011 |

**Diagnosis and main criteria for inclusion:**

Trial indication:

CML (chronic myelogenous leukaemia)

Main inclusion criteria:

- Adult (≥ 18 years) CML patients in the chronic phase
- Medical History of cytogenetically confirmed CML-CP by the presence of the Philadelphia chromosome on bone marrow aspirates (a minimum of 20 metaphases is required; FISH cannot be used); Philadelphia chromosome negative, but BCR-ABL positive CML patients can be included
- ECOG performance status of < 2
- Imatinib treatment for at least 1 year before study entry and showing CCyR or MMR
- Prior treatment with chemotherapeutics such as hydroxyurea or interferon-alpha is allowed
- Prior periods of accelerated phases are allowed
- Negative pregnancy test for female patients of childbearing potential within 7 days before initiation of study drug
- Ability to understand and willingness to sign a written informed consent document prior to any study related screening procedures
- Written informed consent, including the consent to be called for interviews by the external, neutral institution.

Main exclusion criteria:

- Patients with prior blast crisis or stem cell transplantation
- Patients with severe medical condition(s) that in the discretion of the investigator prohibits participation in the study (e.g., clinically significant heart diseases, uncontrolled diabetes, active or uncontrolled infection, impaired gastrointestinal function/diseases)
- Treatment with drugs or substances, especially those known to modify the cytochrome P450 activity, should be either discontinued or exchanged by different medication (see link for complete list of these medications: http://medicine.iupui.edu/flockhart/table.htm.)
- Pregnant or breastfeeding women

- Male or female of childbearing potential unwilling to use contraceptive precautions throughout the trial

**Test product, dose and mode of administration, batch number:**

Test product and mode of administration: Glivec®, p.o.

Dose: 100 mg; 400 mg

Batch numbers: Not applicable. Trade goods.

Since imatinib is approved for the treatment of CML in the study indication it was prescribed according to physician's decision and routine medical practice. There was no study medication supply by Novartis.

**Duration of Treatment:**

Patients were treated for a total of 12 months, 6 months without and 6 months with compliance supporting measures.

**Reference therapy, dose and mode of administration, batch number:**

Not applicable.

**Criteria for evaluation**

**Efficacy: Primary objective:**
The primary variable is the assessment of compliance of the patients by comparison of the number of imatinib (Glivec®) tablets taken before and after intervention.
(as the number of pills taken in relation to the number of pills prescribed in %).

**Secondary efficacy variables:**

- efficacy of imatinib as assessed by PCR testing (as BCR-ABL load in % IS) at months 6, 9 and 12 after study start (at visits 3, 4 and 5, respectively);
- imatinib blood plasma levels during imatinib treatment (as ng/ml) at months 6, 9 and 12 after study start (at visits 3, 4 and 5, respectively);
- assessment of the correlation between the compliance and the efficacy as assessed by PCR testing
- compliance of the patients measured by the BAAS questionnaire using patients answers to the external institution at study start and at months 6, 9 and 12 after study start (at visits 3, 4 and 5, respectively); the items no. 10, 11, 12 and 13 of the score will be coded as "1" for positive answers and "0" for negative answers and summarized for a total score;
- compliance of the patients measured by the MOS questionnaires using patients answers to the external institution at study start and at months 6, 9 and 12 after study start (at visits 3, 4 and 5, respectively); the 9 items of the score will be coded as "1" for positive answers and "0" for negative answers and summarized for a total score; Question 4 has to be inverted before calculating the score;

**Safety:**
Safety assessments consist of evaluating adverse events and serious adverse events and concomitant medications/therapies used to treat them, laboratory parameters including hematology and blood chemistry, body weight and physical examinations.

The crude incidence of adverse events is presented by "System Organ Class" and "Preferred Terms" of MedDRA. The number, seriousness, severity, relatedness, outcome and required action on the investigational medicinal product is described by frequency tables. Serious adverse events are recorded by patient.

**Statistical methods:**

**Efficacy analysis:**

The primary study objective was to compare the efficacy of the compliance supporting interventions on the compliance of the patients, measured by the ratio of taken pills to prescribed pills.

Patients were subdivided into two groups on the basis of the compliance supporting measure chosen (the information service "*Leben mit CML*" – the "Information service group (IS)" – or the use of a daily diary – the "Daily diary group (DD)") at visit 3 (Day 180).

Compliance to study treatment was analyzed by means of descriptive statistics by type of chosen support and overall per treatment period (compliance during the first 6 months of treatment and during the last 6 months of treatment).
The difference in compliance between the two treatment periods was tested using a Wilcoxon signed-rank test and estimates for the difference were calculated using the 95% confidence intervals.
This analysis was performed by type of chosen support and overall. Descriptive statistics were provided for all variables in the summary tables by group. Quantitative variables were summarized by using n, mean, standard deviation (SD), median and range (minimum and maximum). Categorical variables were summarized by using frequency distributions and percentages. Hypothesis testing was carried out at the alpha = 0.05 level for a 2-sided test when comparing treatments. For all inferential analyses, p-value were rounded to three decimal places. Statistical significance was declared if the rounded p-value was less than or equal to 0.05.

Correlation of the compliance to study medication with the efficacy as assessed by PCR testing:

This correlation was assessed by considering the data on the compliance to study medication and the BCR-ABL/ABL (% IS) values. The Spearman's rank correlation coefficient was calculated and presented with its 95% confidence intervals.
This analysis was done by correlating:

- the compliance during the first 6 months of treatment and the BCR-ABL/ABL (% IS) at visit 3 (Day 180)
- the compliance during the first 9 months of treatment and the BCR-ABL/ABL (% IS) at visit 4 (Day 270)
- the overall compliance and the BCR-ABL/ABL (% IS) at visit 5 (Day 360).

BCR-ABL/ABL (% IS) values were summarized at visit 3 (Day 180), visit 4 (Day 270) and visit 5 (day 360) by using descriptive statistics also in order to monitor the efficacy of imatinib.

Furthermore, the correlation at the end of the treatment period was described also in an explorative way by using a linear regression model and was graphically represented.
These analyses were performed by type of chosen support and overall.

**Analysis of Safety**

For the safety analysis the extent of exposure will be summarized both overall and by type of chosen support. The analysis of adverse events will be presented only overall.

Adverse events:
Incidence of treatment-emergent adverse events, adverse drug reactions, serious adverse events, serious adverse drug reactions, severe adverse events and adverse events leading to withdrawal will be provided by using frequency distribution.
The number of TEAEs, SAEs, ADRs, serious ADRs and severe AEs, as well as the number and the percentage of patients experiencing TEAEs, SAEs, ADRs, serious ADRs and severe AEs will be summarized by SOC and PT.
Subjects experiencing more than one TEAE within the same SOC and PT will be counted only once, while two (or more) AEs with the same Preferred Term (PT) will be counted separately.

TEAEs will be summarised by required action by using frequency distributions and will be listed.

**Other planned Analysis**

Correlation of compliance with Imatinib blood plasma levels:
This analysis will be carried out analogously to the one of the correlation between compliance and efficacy as assessed by PCR testing, i.e. it will be assessed by considering the data on the compliance to study medication and the Imatinib blood plasma levels.
The Spearman's rank correlation coefficient will be calculated and it will be presented with it's 95% confidence intervals.
This analysis will be done by correlating:

- the compliance during the first 6 months of treatment and the Imatinib blood plasma levels detected at visit 3 (Day 180)
- the compliance during the first 9 months of treatment and the Imatinib blood plasma levels detected at visit 4 (Day 270)
- the overall compliance and the Imatinib blood plasma levels detected at visit 5 (Day 360).

Furthermore, the correlation at the end of the treatment period will be described also in an explorative way by using a linear regression model and it will be graphically represented.

Evaluation of patient and physician self-assessments:
Evaluation of patient interviews and physician questionnaires was conducted by descriptive statistics. Data was used from patients that were included in the FAS. The distinct answers to each question were added up and presented as percentage of evaluable answers. Missing answers were denoted and marked as not applicable/not specified. Means were presented with standard deviation. BAAS-MOS scales were calculated by summarizing items. Items were summarized for a total score on a patient basis. Means were calculated with standard deviation

(SD). Likert scales were calculated by summarizing numbers and subsequent calculation of means with SD.

**Summary – Results and Conclusions**

Compared to literature the study population showed an above average high baseline compliance. A significant effect of the chosen method to further enhance compliance could not be shown. The chosen method to assess the compliance by pill-counting proved to be problematic in clinical routine practice. The high baseline-compliance within the population indicates a selection of above average managed and informed patients by the study sites. Analysis of patient reported factors and physician reported factors impacting compliance and treatment decisions provide important insight into patient preferences and physician dependent variables that influence quality of care and outcome.

**Efficacy Results**

The **primary endpoint** was compliance to study medication and was compared on an intra-individual basis between the 1st six-months of the study with no intervention to support compliance and the last six months of the study, where interventions to support compliance were applied to patients.

As compliance intervention measures patients could choose an information service initiated by Novartis Germany GmbH ("*Leben mit CML*") or the use of a daily diary as reminder for taking the medication correctly as planned. Compliance to study medication was calculated as the no. of administered tablets as percentage of the prescribed tablets.
54 patients (57.5%) chose the information service (IS-group) and 33 patients (35.1%) preferred the daily diary (DD-group). 7 patients (7.4%) used both methods.

**Table 4:** Compliance to study medication

| Compliance (%) | IS - group N=54 | DD - group N=33 | IS -& DD-group N=7 | Overall N=94 |
|---|---|---|---|---|
| **During the first 6 months of treatment** | | | | |
| Mean (SD) | 98.22 (10.93) | 98.45 (8.38) | 96.39 (5.48) | 98.17 (9.72) |
| Range | 43.5-127.8 | 76.8-131.0 | 86.1-100.0 | 43.5-131.0 |
| **During the last 6 months of treatment** | | | | |
| Mean (SD) | 100.28 (4.48) | 96.59 (8.81) | 98.39 (7.49) | 98.84 (6.69) |
| Range | 83.0-112.2 | 64.9-110.9 | 82.4-106.0 | 64.9-112.2 |
| **Difference in compliance between periods** | | | | |
| Mean (SD) | 2.05 (12.98) | -1.86 (12.02) | 2.00 (6.52) | 0.68 (12.33) |
| Range | -29.3-66.2 | -43.5-26.8 | -8.9-11.9 | -43.5-66.2 |
| Wilcoxon signed-rank test: p-value | 0.055 | 0.674 | 0.438 | 0.164 |

The mean compliance exceeded 96% in all groups already in the first 6 months without any interventional support, leaving very little space for improvement.
Patients with the information service improved their compliance during the second 6 months to a mean value of 100.3%, (n.s.) whereas in patients using the daily diary the mean value dropped to 96.6% (n.s.).
The improvement of 2% in the IS-group reaches a p-value of 0.055 (Wilcoxon signed-rank test). No evidence of an influence of the daily diary on compliance could be found (p=0.67). For the 7 patients who used both methods, an improvement of 2% could be seen (p=0.44).

For the **secondary endpoints**, no correlation between the compliance and the BCR-ABL (% IS) levels for any of the study period and the Imatinib blood plasma levels (ng/ml) for the first 6 and 9 months of the study could be detected.

Patients of the IS-group showed a slight increase in the BCR-ABL (% IS) levels from day 180 to the end of the study, whereas patients of the DD-group showed a decrease. Both changes were marginal and clinically not relevant.

For the total study duration, a significant negative correlation between compliance and Imatinib blood plasma levels (ng/ml) was calculated, as the 95%CI does not include the “Null”-value. This effect was not present in the DD-group and in patients using both methods.

Patients of the IS-group showed an increase in the Imatinib blood plasma levels (ng/ml) from day 180 to the end of the study, whereas patients of the DD-group showed a decrease.

**Correlation of the compliance to study medication with the efficacy as assessed by PCR testing**

No correlation between the compliance and the BCR-ABL/ABL (% IS) levels could be detected for any of the study periods (Table 5). The 95%-confidence intervals of all coefficients of the Spearman rank-correlation include the “Null”-value.

**Table 5:** Correlation between compliance to study medication and PCR testing

| | IS - group N=54 | DD - group N=33 | IS -& DD-group N=7 | Overall N=94 |
|---|---|---|---|---|
| **First 6 months of treatment** | | | | |
| Compliance to study medication (%) | | | | |
| Mean (SD) | 98.22 (10.93) | 98.45 (8.38) | 96.39 (5.48) | 98.17 (9.72) |
| Molecular analysis – BCR-ABL/ABL (% IS) – at visit 3 (Day 180) | | | | |
| n | 50 | 31 | 7 | 88 |
| Mean (SD) | 0.0122 (0.0311) | 0.0146 (0.0254) | 0.0093 (0.0123) | 0.0128 (0.0279) |
| correlation coefficient * (95% CI) | 0.000 (-0.278,0.278) | -0.026 (-0.377,0.332) | 0.472 (-0.468,0.896) | 0.018 (-0.192,0.227) |
| **First 9 months of treatment** | | | | |
| Compliance to study medication (%) | | | | |
| Mean (SD) | 101.26 (12.99) | 97.81 (6.14) | 97.26 (5.83) | 99.75 (10.70) |
| Molecular analysis – BCR-ABL/ABL (% IS) – at visit 4 (Day 270) | | | | |

| | | | | |
|---|---|---|---|---|
| n | 51 | 32 | 7 | 90 |
| Mean (SD) | 0.0157 (0.0427) | 0.0099 (0.0286) | 0.0061 (0.0082) | 0.0129 (0.0364) |
| correlation coefficient * (95% CI) | -0.008 (-0.283,0.268) | -0.141 (-0.465,0.221) | 0.593 (-0.334,0.924) | 0.008 (-0.200,0.214) |
| **Overall treatment (12 months)** | | | | |
| Overall compliance to study medication (%) | | | | |
| Mean (SD) | 100.77 (8.76) | 97.76 (7.02) | 97.21 (5.51) | 99.45 (8.06) |
| Molecular analysis – BCR-ABL/ABL (% IS) – at visit 5 (Day 360) | | | | |
| n | 53 | 31 | 7 | 91 |
| Mean (SD) | 0.0326 (0.1918) | 0.00449 (0.0076) | 0.0028 (0.0044) | 0.0207 (0.1465) |
| correlation coefficient * (95% CI) | -0.038 (-0.305,0.235) | -0.052 (-0.398,0.309) | 0.408 (-0.524,0.881) | 0.045 (-0.163,0.248) |

* Spearman rank

Patients of the IS-group showed an increase in the BCR-ABL/ABL (% IS) levels from day 180 to the end of the study, whereas patients of the DD-group showed a decrease (Figure 1).

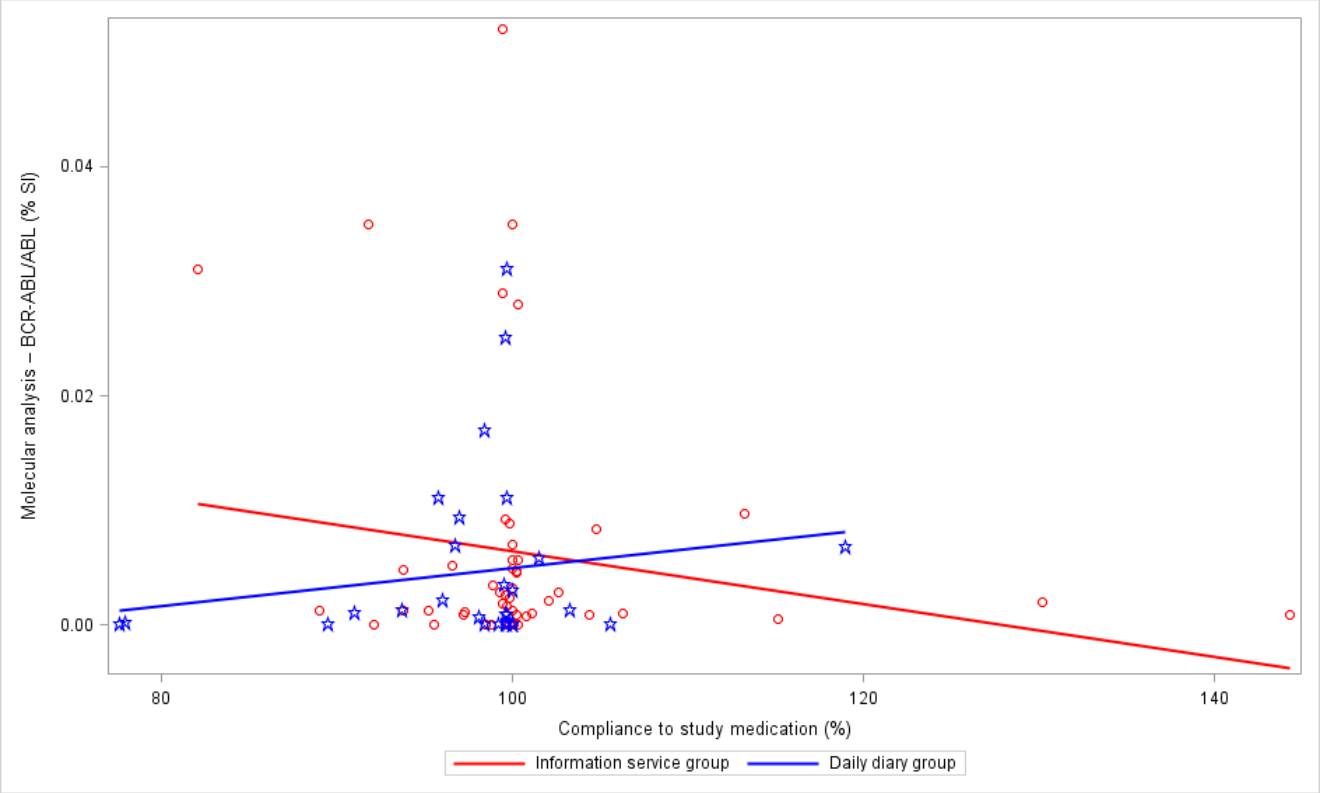



**Figure 1:** Correlation of compliance and BCR-ABL/ABL (% IS) for the total study period at visit 5

**Results from Analysis of Patient and Physician Perceptions on Self-assessment and Adherence Impacting Factors**

Analysis of the BAAS-MOS and Likert scale revealed a high compliance at baseline with values close to maximum achievable values. Only marginal changes could be observed and the high compliance sustained throughout the study run-time.

In addition, the patient-physician relationship was reported to be the most valuable source to support patient adherence. Other sources to get information, e.g. the internet were of lower importance. The majority of patients felt well informed and medicated. Patients who reported to be not well informed, did not desire further information even upon request.

The most important information tools to provide a high quality treatment in relation to physicians, are continuous training on conferences and guidance by guidelines. Brochures of pharmaceutical manufactures and other sources of information were of lower importance.

**Treatment compliance by patient interviews**

The evaluation of compliance reported by patients was concentrated to changes from V1 to V5 in the Basel-scale (BAAS), the Morisky-Scale (MOS) and the Likert-Scale. Analysis of patient interviews was conducted by descriptive statistics. Data was used from patients that were included in the FAS. The evaluation of compliance by the BAAS, MOS and Likert Scale revealed no significant change in compliance as reported by the patient.
As ascertained by pill-counting the high baseline compliance of the patients in the study population was also reflected by the patient interviews. The values determined at baseline were already close to the maximum achievable values for compliance for all three measures (Basel Scale: 4; Morisky Scale: 9 and Likert-Scale: 10) and sustained their high level throughout the entire study run-time (figure 2).

**Figure 2: Compliance as assessed by patient interviews**

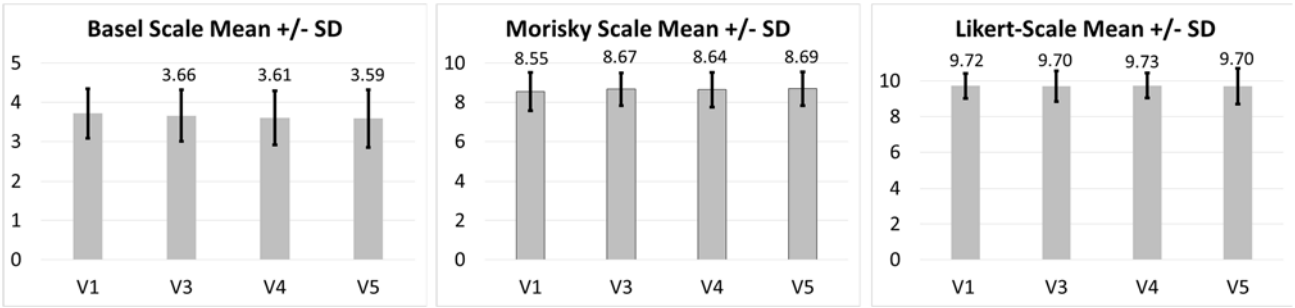



Figure 11-3: Evaluation of compliance by Basel Scale, Morisky Scale and Likert Scale. The number of evaluable questionnaires for the Basel Scale were $n_{V1}$= 95; $n_{V3}$= 89; $n_{V4}$= 93; $n_{V5}$= 93, for the Morisky Scale $n_{V1}$= 95; $n_{V3}$= 90; $n_{V4}$= 94; $n_{V5}$= 94 and for the Likert Scale $n_{V1}$= 95; $n_{V3}$= 90; $n_{V4}$= 94; $n_{V5}$= 93, respectively. Data are presented as mean +/- SD.

The patient-physician relationship was reported to be the most valuable source to support patient compliance. Other sources to get information, e.g. the internet were of lower importance. The majority of patients felt well informed and medicated. Patients who reported to be not well informed, did not desire further information even upon request. The most important information tools to provide a high quality treatment in relation to physicians, are continuous training on conferences and guidance by guidelines. Brochures of pharmaceutical manufactures and other sources of information were of lower importance.

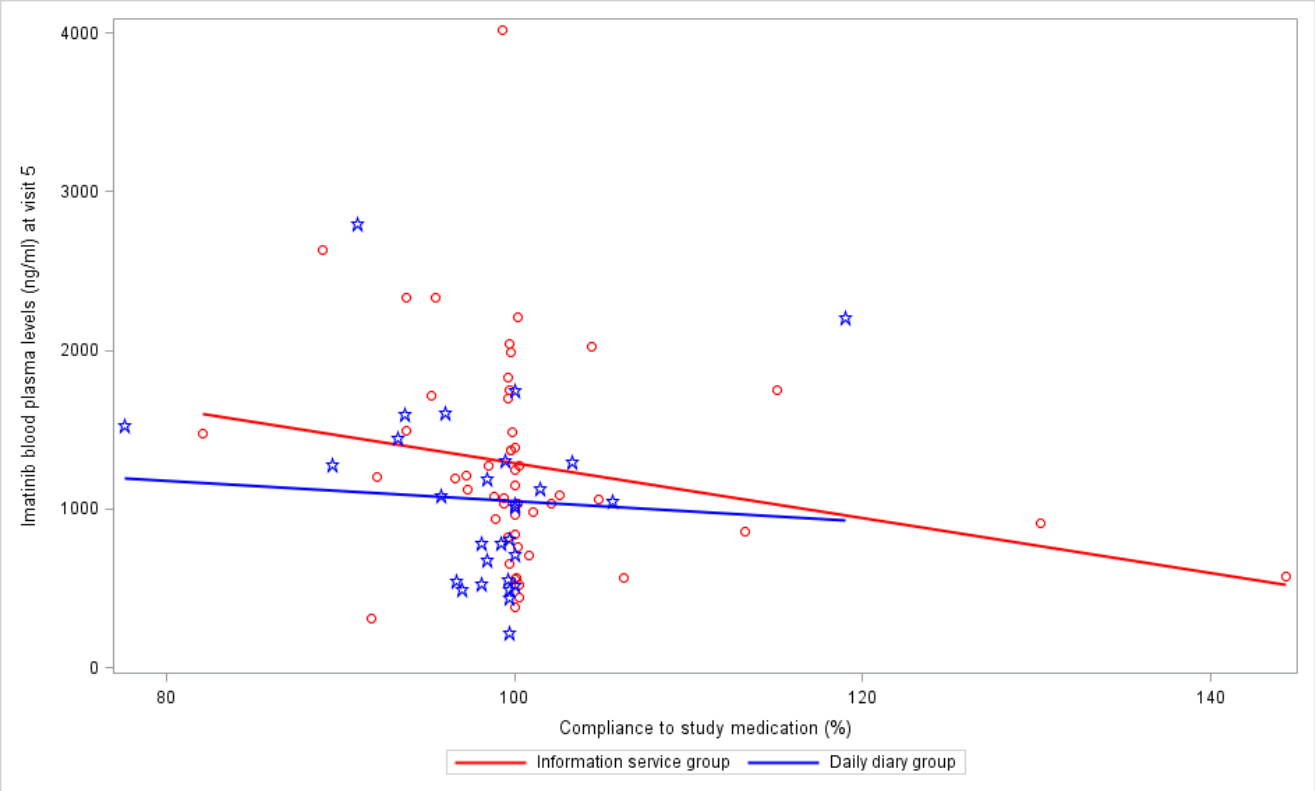
**Correlation of compliance with Imatinib blood plasma levels**

No correlation between the compliance and the Imatinib blood plasma levels (ng/ml) could be detected for the first 6 and 9 months of the study. The 95%-confidence intervals of all coefficients of the Spearman rank-correlation include the “Null”-value.

For the total study duration, a significant negative correlation between compliance and Imatinib blood plasma levels (ng/ml) was calculated, as the 95%CI does not include the “Null”-value. This effect was not present in the DD-group and in patients using both methods.

Patients of the IS-group showed an increase in the Imatinib blood plasma levels (ng/ml) from day 180 to the end of the study, whereas patients of the DD-group showed a decrease (Figure 3).

**Figure 1:** Correlation of compliance and Imatinib blood plasma levels (ng/ml)




## Safety Results

Per inclusion criteria, all patients had already been on study medication for a minimum of one year prior to study entry. The safety population included all patients receiving at least one dose of the investigational product and for whom any data or information about the time after the first dose of investigational product is available (Safety-Set = 106 patients). The safety profile was unremarkable with a total of 33 patients (31%) with adverse drug reactions and 10 patients (9.4%) reporting severe adverse events. Serious treatment-emergent adverse events in 10 patients by system organ class are provided in table 6. One death was reported for patient 0110012. The patient was a 76 year old female who received 400 mg imatinib. She deceased due to a sudden cardiac event. A relation to the study drug was not suspected

**Table 6:** Serious Treatment-emergent adverse events by system organ class

| System Organ Class<br>Preferred Term | Number (%)<br>of patients | Number of<br>events |
|---|---|---|
| Gastrointestinal disorders | 3 (2.8%) | 4 |
| Abdominal pain | 1 (0.9%) | 2 |
| Diarrhoea | 1 (0.9%) | 1 |
| Pancreatitis | 1 (0.9%) | 1 |
| Nervous system disorders | 3 (2.8%) | 3 |
| Haemorrhage intracranial | 1 (0.9%) | 1 |
| Hemiparesis | 1 (0.9%) | 1 |
| Transient ischaemic attack | 1 (0.9%) | 1 |
| Injury, poisoning and procedural complications | 2 (1.9%) | 2 |
| Femur fracture | 1 (0.9%) | 1 |
| Fracture | 1 (0.9%) | 1 |
| Hepatobiliary disorders | 1 (0.9%) | 1 |
| Cholelithiasis | 1 (0.9%) | 1 |
| Investigations | 1 (0.9%) | 1 |
| Norovirus test positive | 1 (0.9%) | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.9%) | 1 |
| Prostate cancer | 1 (0.9%) | 1 |
| Cardiac disorders | 1 (0.9%) | 1 |
| Cardiac failure | 1 (0.9%) | 1 |
| Surgical and medical procedures | 1 (0.9%) | 1 |
| Cardiac pacemaker insertion | 1 (0.9%) | 1 |
| Vascular disorders | 1 (0.9%) | 1 |
| Peripheral ischaemia | 1 (0.9%) | 1 |

Note 1: A serious AE in an event judged as serious, i.e. the option “Mark if AE meets definition of serious” = “Y” in the CRF.

**Conclusion**

There seems to be a positive effect of an information service on compliance. Statistical significance was not reached due to the reduced number of patients included in the study compared to the original sample-size estimation of the study protocol.

The method of daily diaries could not be shown to improve compliance.

Key finding from BAAS-MOS and Likert scales are in accordance with observations of pill-counting. A high baseline compliance was revealed by the patient interviews that sustained throughout the entire study. Success to therapy requires a pronounced patient-physician relationship. The high baseline compliance along with the self-assessment of the patients

indicates an excellent patient-physician relationship of patients and study sites. Further information might be of advantage in individual cases but should not be overemphasized. A subgroup of patients demanded solely information by patient-physician relationship and emphasizes the impact of a guideline-based therapy by the treating physician. The importance of training opportunities of physicians by participation to conferences and the impact of guideline-based therapy are confirmed by the study.
The safety analysis did not reveal any previously unknown safety signals for imatinib treatment.

**Date of report**

18.06.2014

**Substantial Protocol Amendments**

3 amendments have been applied to the study of which one was substantial (amendment 3).

Amendment 3 concerned stopping recruitment to avert an exceeding of the planned project runtime and therefore to prevent an endangering of the study goals. The rational was that enrollment was beyond target. Only half the number of intended sites and patients could be recruited and enrolled, respectively in a period of nearby 24 months.
Further enrollment of patients was considered unlikely at that point, as study sites had reached the limit of their enrollment potential. In addition ongoing replacement of Imatinib (Glivec® = trial drug) to Nilotinib (Tasigna®) over the last few years as a first line therapy for the treatment of CML patients further added to the effect of reduced patient enrollment into this trial. Because of that reasons, the enrollment of patients into this trial was stopped. Ongoing patients (46 at time of recruitment stop) have been treated as per protocol.