Study Design
We pooled data from 4 double blind, randomised, 3-period, crossover studies; in healthy volunteers. Subjects went through three periods of: free smoking, enforced abstinence with an active treatment (different in each study) and enforced abstinence with placebo. Each period consisted of 3 days (72 hours) of observation.

The Smoker Complaint Scale (SCS) [1] was self-administered at predefined times, over the 3-day period, for smoking withdrawal symptoms assessment. The 3-day of abstinence corresponding to placebo or active treatments were preceded by a run in period of placebo/active administration, ranging from half a day to 14 days (figure 1). There was a wash-out of at least 10 days between each treatment period. We report methods and results to explore if a factorial structure could be identified in the SCS and if this could lead to a further strengthening of this questionnaire.

Methods
A total of 113 healthy subjects not intending to quit smoking were recruited from the panel of volunteers of the Clinical Pharmacology Unit of GlaxoSmithKline in Verona (Italy). Main inclusion criteria were: at least 18 years old, have smoked an average of 15 cigarettes or more a day for the past year, have a Fagerstrom Tolerance Questionnaire (FTQ) scores of at least 7, have signed a dated written informed consent prior to study participation. Main exclusion criteria were: drug or alcohol abuse; use of long term medication; use of any drug within the previous 4 weeks, current use of any nicotine replacement therapy. Ethical committee approval was obtained before the start of each study, which was conducted in accordance with the Declaration of Helsinki.

Procedure Subjects that received active or placebo treatment quit smoking abruptly at 7:30 am of day 1 of observation. Measurements and Evaluations Time Zero (t0), around 8 am, was the beginning of abstinence, 30 minutes after the subject’s last cigarette allowed. The SCS was self-administered at t0, 3, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours to evaluate cigarette withdrawal symptoms. Each item consists of 20 items scored on a likert scale from 1 (very definitely not) to 7 (very definitely). These are summarised by means of a Sum Total Score, ranging from 20 to 140, where higher scores represent higher levels of withdrawal symptoms. Each item captures a different smoking withdrawal symptom (table 1). Breath Carbon Monoxide (CO) and Saliva Cortisone were assessed at 0.6, 12, 24, 30, 36, 48, 54, 60 and 72 hours to evaluate smokers’ smoking status and abstinence compliance (figure 2).

Statistics
The score of each SCS item was at first summarised over the 72 hours course for each of the weighted mean. This was calculated as the area under the measurement-time curve, using the linear trapezoidal method, divided by the time over which the measurements were taken.

The pooled set of 72-h weighted mean for each SCS item was randomly split into 2 subsets. One, consisting of 19 observations, was used for the Exploratory Factor Analysis (EFA) to identify a Factors structure of the SCS. The other, of 158 observations, was used for the Confirmatory Factor Analysis (CFA) to examine the validity of the hypothesised Factors previously identified [2-3].

EFA consisted of Principal Component Analysis. Decisions regarding the number of factors to extract were based on the results of the Scree test. CFA was performed by means of Structural Equation Models (SEM) analyses, also called LISREL. Different Factor models were tested, on the basis of a variety of fit measures, with the aim of achieving the model that provides the best fit to the observed data. Finally, both Reliability and Validity (Convergent and Discriminant) of the new Factors were assessed. All analyses were performed using SAS Version 8.2 for Windows System and Procedures.

Results
Relevant study population characteristics are reported on table 2. The EFA recognized 4 main Factors accounting for 95% of the total variance (table 3). Factor 1, clustered by 9 items (“anxious”, Q1, “irritability”, Q2, “fluctuations in mood”, Q4, “depressed”, Q5, “left out”, Q6, “headache”, Q7, “hunger”, Q8) and represents the broad nature of “Nervousness”, (correlation of 0.81 between items “Nervousness”, “headache”, “left out”, “hunger”, “irritability”, “fluctuations in mood”, and “depressed”). Factor 2, clustered by 4 items (“confusion”, Q3, “sleeping”, Q4, “food”, Q5) identifies concern over “confusion” and “sleep”. Factor 3, clustered by 4 items (“craving”, Q6, “urge to smoke”, Q7, “craving cigarettes”, Q9), captures the concept of “Craving”. Factor 4, clustered by 4 items (“comfort”, Q10, “urge to smoke”, Q10, “urge to smoke”, Q10) identifies concern for “comfort”. Further, the correlation analysis confirmed the improvement in the Model fit after the Confirmatory Factor Analysis (CFA). Furthermore this analysis confirmed the improvement in the Model fit after the extraction from Factor 1 of a relevant subset of 4 items (“depressed”, Q5, “left out”, Q6, “hunger”, Q8) which may relate more specifically to the concept of Depression (figure 3). All these 4 Factors (Nervousness, Confusion, Craving and Depression) showed significant levels of reliability (Cronbach’s α and Index of Composite Reliability ≥ 0.90) (table 4) and construct validity (convergent Factor loadings p<0.01, discriminant r ≤ 0.90) (figure 4).

Discussion/Conclusions
A questionnaire on specific signs of smoking/nicotine withdrawal symptoms is difficult to reach. For example the two most mentioned were the Surgeon General’s Report (USDHHS 1988) [4] and the American Psychiatry Association with its Diagnostic and Statistical Manual (DSM IV, 1994) [5], in part, derived in a review of the literature on nicotine withdrawal symptoms. However, as already reported the different methodology used to investigate the effect of smoking abstinence on smoking withdrawal symptoms is faced with different findings. Among these methodological discrepancies, relevance is given to the assessment of abstinence symptoms by means of single-item questionnaires, may be an able to capture aspects of abstinence symptoms experienced by individuals in different stages of drug dependence and in different environmental conditions. Moreover, single-item questions may not reflect the theoretical perspectives of the nature of that specific symptom [6-8]. The SCS is a questionnaire validated and reliability used to assess smoking withdrawal symptoms [9]. However, as outlined above, the improvement of existing scales, the generation of new tools and the achievement of a consensus in the definition of withdrawal symptoms, is a constant objective in the field of smoking dependence [10-13]. In this light, the novel approach of a factorial structure could be identified in the SCS and if this could lead to a further strengthening of the questionnaire. The result shows the first time, that the 20 items of the SCS might be summarised by a 4-Factor Model, comprising dimensions of Nervousness, Confusion, Depression and Craving. In our view, the recognition of these 4 Factors may increase the strength of the SCS for three main reasons: (i) the specific dimensions of the smoking withdrawal syndromes can be studied separately; (ii) the impact of each subscale dimension on the overall abstinence syndrome (Sum Total Score) can be detected; (iii) differentiated changes over time of each factor could be monitored.