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Annex I:
Answer to the negative Opinion of EMEA on Ukrain, dated 12th of June 2007

This answer by Now Pharm AG refers to the following EMEA documents:

- Letter to Dr Nowicky, Doc.Ref. EMEA/248362/2007, dated 12june07, signed Prof. Vamvakas, Acting Deputy Head of Sector Scientific Advice and Orphan Drugs, 1p,
- Opinion of the Committee for Orphan Medicinal Products on orphan medicinal product designation, Doc.Ref. EMEA/COMP/234369/2007, dated 31may07, signed Dr Westermark, Chairperson of COMP, 1p,
- Annex I, Grounds for the opinion on orphan medicinal product designation, Doc.Ref. EMEA/COMP/234369/2007 0.4 current (undated), 3p,
- EMEA/COMP Summary report on an application for orphan medicinal product designation chelidonii radix special liquid extract, EMEA/OD/002/07, Doc.Ref. EMEA/COMP/96936/2007 final, dated 31may07, 18p,

Above mentioned documents have been received on 13jun07.

As the above mentioned summary report contains the most detailed explications for the negative opinion of the EMEA Committee for Orphan Medicinal Products (COMP), these points of criticism are answered in the order of the respective EMEA document (EMEA/COMP/96936/2007 final).

To summarise, the COMP is of the opinion that:

- *"the medicinal product does not satisfy the criteria for designation as set out in the first paragraph of Article 3(1)(a), Regulation (EC) no 14/2000 of 16 December 1999;*
- *"the sponsor has not established, as required under Article 3(1)(b), Regulation (EC) No 141/2000 of 16 December 1999, that the above-mentioned product will be of significant benefit to those affected by the condition in question for which a satisfactory method of treatment has been authorised in the community".*

COMP, having examined the application, concluded:

- Pancreatic cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening due to a very poor overall survival;
- satisfactory methods of treatment of the condition have been authorised in the Community, and the sponsor has not provided sufficient justifications that chelidonii radix special liquid extract may be of significant benefit to those affected by the condition, over currently authorised treatments for pancreatic cancer, neither through better efficacy, better safety, or a significant contribution to patient care.

Therefore, EMEA concludes that Now Pharm "*has not provided sufficient justifications that chelidonii radix special liquid extract (in short Ukrain) may be of significant benefit, ... neither through better efficacy, better safety or a significant contribution to patient care*".

Now Pharm disagrees and objects that this opinion, in particular of the EMEA expert Prof. Winkler, does not consider all details of the documents provided that describe clinical experiences with Ukrain. When comparing the arguments of EMEA with those of Prof. Winkler, ad personam, it is easy to recognise that his opinion has influenced the decision of EMEA. A number of EMEA statements are incorrect, incomplete and not objective as is outlined below:

Ad:

I Administrative Data

Although it is correct to mention that two applications for marketing authorisation were filed in Austria, it has to be stressed that on both occasions it was Prof. Winkler who has made a negative assessment on Ukrain. Prof. Winkler had therefore already a negative and biased opinion before the EMEA-COMP procedure had started. Despite of new data since that, he maintained exactly the same arguments. Clinical results in favour of Ukrain were ignored and even not commented.

Ad:

II Background on the Product

Ad 1) Proposed indication

No comments.

Ad 2) Main features of disease/condition

No comments.

Ad 3) Active substance and pharmacological class and mode of action

The background description given by EMEA is correct. However, some statements are incorrect: On p.6/18, EMEA refers to "*data submitted by the sponsor in previous applications*" and concludes that "... *TERTIARY alkaloids may be contained in the end product*". This is certainly not correct. The sponsor has explained that alkaloids are exclusively in quaternary

form as has been discussed during the oral meeting. It is reminded that during the manufacturing process a crystalline precipitate is obtained which is immediately diluted in water; tertiary alkaloids do not form a crystalline product, only salt forms of alkaloids; a quaternary structure is however a pre-requisit for a salt form). On p.7/18 it is stated that "*no reference is made to spectroscopy data or other chemical methods of quality assessment to support the statement that no free Thio-TEPA or aziridine ring compounds can be detected*". This is also not correct; the final product Ukrain does not contain any free Thio-TEPA. It is reminded that the reason for EMEA's (first) rejection - lack of information on the substance Ukrain® itselfs - has been completely resolved by LAT's thorough analysis, as proven and confirmed by EMEA (second opinion). Chelidonium contains tertiary alkaloids (like protopine, allocryptopine, chelindonine, homechelidonine) and quaternary alkaloids (e.g. like sanguinarine, chelerythrine), in the final product, Ukrain, alkaloids are in quaternary form only; Now Pharm is surprised that this is again an issue, as this topic was not discussed during the last meeting.

This is even more confusing as on page 6/18 EMEA concludes that "*no free Thio-TEPA or aziridine ring compounds can be detected in NSC 631570. Ukrain is therefore definitively different from the starting materials*". From this it is delineated that EMEA accepts (page 8/18) the opinion of the sponsor: "*the previously findings that the drug possesses other pharmacological properties compared with the start components for its synthesis seem confirmed*" (compare this with comments of Prof. Winkler later on where he argues that Ukrain must have the same potentially hepatotoxic properties as the crude, herbal extract).

On page 8/18 EMEA fails to acknowledge that Ukrain has a unique mechanism of action that is definitively different from other medicinal products. In short, Ukrain induces apoptosis of cancer cells by inhibition of the polymerisation of tubulin; this results in a stop of cell growth in the G2M-phase. This mechanism is clearly different from that of gemcitabine (an analogon of pyrimidine; instead of cytidine, gemcitabine-triphosphate is build into the DNA-helix and DNA-synthesis stops) as well as of erlotinib (which is a selective inhibitor of tyrosine-kinase; cell growth is stopped by blocking the transmission of growth signals via the human epidermal growth factor receptor).
Ukrain has therefore an innovative mechanism of action, different of the action of these two medicinal products. In contrast to these other medicinal products, Ukrain is not toxic to healthy tissues as demonstrated by in vivo tests and the fact that Ukrain can be (safely) injected intramuscularly. Despite that this is clearly a safety benefit this has not been acknowledged and commented by EMEA.

Ad 4) Present stage in drug development

Ad study: Zemskov et al, 2002 (p10/18):

The study by Zemskov et al. (2002) does not specify the statistical methods employed for the analysis; indeed, no statistical comparison was performed between the two groups, there being only descriptive results. Histology is also not well described. There is confusion on the objectives: although the authors claim in the introduction that they intended to evaluate Ukrain "in controlling the growth of pancreatic cancer, and improving the quality of life", in the abstract and in the results much more prominence is given to survival data. There is no clear definition of the primary endpoint, sample size calculation, and estimation of the expected effect of the drug. Although the Authors state that they intended to evaluate patients "in the late stages of this disease where prognosis is extremely poor", the studied group included patients with very different stages, from II to IV. Also, although this study is placebo-controlled, only patients who refused chemotherapy were enrolled, and where then given a choice between placebo and an active treatment (Ukrain); this is likely to introduce selection bias and undermine the external validity of the results.

"The study does not specify the statistical methods ..."

This EMEA statement is incorrect and misinterprets the publication. The EMEA opinion argues that "*no statistical comparison was performed between the two groups ... being only descriptive results*" (p.10/18). This is not correct as the publication gives the Kaplan-Meier survival curves of both groups and states that a log rank test was performed (p.86: "Survival was calculated using the log-rank test").

"histology is also not well described ..."

The authors think that for such aggressive disease as pancreatic cancer histological specification "pancreatic carcinoma" is enough to understand the prognosis for these patients.

"there is confusion on the objectives ..."

The EMEA reviewers should better describe this as confusion on the results but not as "confusion on the objectives". The primary objective of the authors was of course to evaluate Ukrain "in controlling the growth of pancreatic cancer, and improving the quality of life". Because of past (negative) experience of pancreatic cancer treatment and being the leading institution in the Ukraine concerning pancreatic cancer treatment the authors did not expected that a drug derived from a plant could prolong life in such aggressive disease as pancreatic cancer where already many chemotherapeutic agents have shown no success and sometimes (as in the case of 5-FU) also lead to worsening of prognosis. When analyzing the results the authors saw the effects on survival. Scientifically and ethically it seems to be justified to focus in the publication on survival than on quality of life.

"Patients ... were then given a choice ..."

In addition, the EMEA opinion states that "*patients ... were given a choice between placebo and active treatment (Ukrain); this is likely to introduce selection bias and undermine the external validity of the results*". As this study was a placebo-controlled study, only patients could be recruited that refused chemotherapy for ethical reasons. The statement is further incorrect, misleading and misinterpreting the publication as it suggests that PATIENTS made the choice between placebo and Ukrain which was not the case. In addition, the idea, that bias could be introduced because only patients that had refused chemotherapy have been included is completely wrong. It is strange that reviewers expect that pancreatic cancer patients who refused chemotherapy have better prognosis than patients that do not refuse chemotherapy. With the same argument one could speculate that EACH clinical trial is biased simply by the fact that only patients WILLING to participate to a clinical trial (obviously a subgroup of the whole population) and giving their consent are recruited.

It is correct that other points are not described in more details due to the fact that publishers want to shorten manuscripts. However, for the sake of good orders data of the two groups are summarised again to demonstrate that only 3 patients (two of which in the placebo arm!) were of stage 2; the large majority of patients suffered from advanced pancreas carcinoma:

Patient Characteristics

	Ukrain + Vitamin C	**Vitamin C**
Location in pancreas body	2 (10%)	4 (19%)
UICC Stage 2	1 (5%)	2 (10%)
Stage 3	5 (24%)	5 (24%)
Stage 4a	8 (38%)	9 (43%)
Stage 4b	7 (33%)	5 (24%)
Sex M / F	17 / 4	10 / 11
Age (y)	60.7	65.4
Prior Therapy	none	none
Signs of biliary obstruction	19 (90%)	18 (86%)
Gastric obstruction/bypass	3 (14%)	4 (19%)
Metastases, liver	5 (23.8%)*	3 (14.3%)
peritoneal	2 (9.5%)	3 (14.3%)
other	1 (4.8%)	- (0%)

* includes patients with liver – and peritoneal metastases

Now Pharm concludes that the EMEA opinion contains serious errors; EMEA did not consider the data presented in this publication in a correct and objective way; the opinion distorts the publication.

The EMEA opinion does also not comment on the excellent safety / tolerance of Ukrain.

Ad study: Gansauge et al, 2002 (p10/18):

> The inclusion criteria in the Gansauge et al. (2002) study are unclear; in particular, the staging criteria of the patients before inclusion are not specified, and similarly whether endoscopy was performed on all patients, whether there was pre-treatment blinding, etc. No statistical methods are cited in the article, regarding randomisation or analysis of the data. There is no power estimation or sample size calculation, and the primary endpoint is unclear. Also, there seems to be bias introduced during the study, as response was evaluated only in patients who had an increased Ca19.9 level or who were alive at the time of re-evaluation. Patients in Arm A (gemcitabine only) received less treatment cycles than those in arm B (Ukrain) and arm C (Gemcitabine + Ukrain), and for arm C this difference is statistically significant; the authors do not discuss this discrepancy, which can profoundly affect the results of the clinical trial. Finally, in the Ukrain only group, almost one third of patients had been treated for less than 3 months at the time of the evaluation of results, which renders the survival data unreliable.

"... ***there seems to be bias introduced ..., as response was evaluated only in patients who had an increased Ca19.9 level or who were alive at the time of re-evaluation"***

"The inclusion criteria ... are unclear"; ... staging criteria ... are not specified, ...".

Selection criteria are clearly described (section: "Patients and methods"); inclusion criteria were histologically proven unresectable adenocarcinoma of the pancreas. Exclusion criteria are also given in details. Staging criteria are specified as well (UICC), which are internationally accepted criteria, and presented in details. As has been explained before, no publication can describe all details of a study because of restrictions by publishers.

"... whether there was pre-treatment blinding ..."

In oncology, double blind clinical trials are not always possible. On the other hand, clinical trials in oncology use objective endpoints that are hardly influenced by the physician or patient such as response and survival. The level of "bias" in the studies with Ukrain is therefore not different from most other clinical trials on tumour patients.

"...Patients in Arm A (gemcitabine only) received less treatment cycles ..."

EMEA opinion misinterprets also some other facts of this publication: The publication states "Compared with the gemcitabine monotherapy, significantly more cycles were applied in the gemcitabine/NSC631570 arm". This is distorted by the EMEA opinion to: "*Patients in Arm A (gemcitabine only) received less treatment cycles than those in arm B (Ukrain) and arm C (Gemcitabine + Ukrain)*". On the arm "Ukrain" the authors made no statement or further comments because 13/30 patients were still under therapy.

"Less treatment cycles" have a trivial explanation: If chemotherapy is discontinued by the treating physician this is commonly done for two main reasons: tumour progression or side effects of therapy. The response evaluation after 3 months shows that 67.8% of the patients of the Gemcitabine group (in contrast to 25% and 17.9% that received Ukrain or the combination) had progressive disease, which explains therefore "*less treatment cycles*". If "*less treatment cycles profoundly affect the results*" as stated in the EMEA opinion, this ignores the fact that continuation of a treatment that is not effective is unethical! Less treatment cycles are also not a mathematical factor that enters in the calculation of Kaplan-Meier survival curves. Similar, **a percentage of patients that had not finished their planned treatment duration (Ukrain only group) could only induce a less favourable result for the Ukrain-receiving group of patients but not the inverse!**

The conclusion of EMEA opinion that "*response was evaluated only in patients who had an increased Ca19.9 level*" and "*one third of patients had been treated for less than 3 months at the time of the evaluation of the results*" is not substantiated. The basis of this (mis)interpretation of the publication by EMEA remains unclear.

The EMEA opinion focuses on (clinical) response without considering at all the hard endpoint overall survival. The criticism that (clinical) response was evaluated only on patients who were alive is amazing because this is a common procedure. The publication clearly states that "patients who died prior to the first re-evaluation were considered PD (progressive disease)". In contrast to the response-focussed position of the EMEA opinion, **it has to be stressed that the endpoint overall survival presented by the authors is bias-free**. The Kaplan-Meier survival plots (which are independent on the number of cycles) and which are a standard method for comparing median survival are given in the publication but EMEA fails to comment upon. Clinical results demonstrate a statistically significant advantage of BOTH groups receiving Ukrain ($p < 0.01$ vs Ukrain and <0.001 vs. Ukrain + Gemcitabine).

It is a major weakness in the interpretation of these results by EMEA to have ignored significant prolongation of survival.

Now Pharm concludes that the EMEA opinion is biased; it does not reflect the information provided in the publication; it is not objective because it does not consider this publication in important details, in particular the statistically significant superiority of both arms receiving Ukrain in terms of survival.

Ad study: Aschhoff 2003:

> The study by Aschoff (2003) is a retrospective study. The inclusion and allocation criteria are not specified, so bias cannot be excluded. The staging of the disease before and after treatment is not specified, and neither are the evaluation criteria (WHO? RECIST? others?). Also, criteria for evaluating toxicity are not specified.

"The inclusion and allocation criteria are not specified so bias cannot be excluded".

Concerning the publication of **Aschhoff** (2003), the above mentioned statement "*The inclusion and allocation criteria are not specified so bias cannot be excluded*" neglects important facts: Although staging is not specified, the publication clearly says that this sample of 28 patients was recruited between August 1997 and December 2003 and consisted of 21 patients unresponsive to Gemcitabine and 5-FU and of 7 patients that refused chemotherapy ("All the patients presented with advanced and/or metastatic disease, making surgical tumour eradication impossible. Of the patients, 21 had previously been treated with 5-fluorouracil or gemcitabine but due to disease progression this therapy had been discontinued"). From that it can be concluded that at least 21/28 patients were already in an advanced stage and had exhausted all therapeutic options.

As to the "*allocation*", it is against common sense to believe that a centre receiving patients for palliative treatment excludes any of them from therapy; given the fact that pancreatic cancer is a rare disease, one can safely assume that 28 patients represent the total number of patients seen at this centre during this relatively short period of roughly 64 months, even if this is not expressly written in the publication. This represents therefore a population that has NOT been selected; the EMEA opinion is thus unsubstantiated; there is absolutely no basis for the assumption that "*inclusion and allocation criteria*" have been applied. On the contrary, it can be safely assumed that this population has not been selected, and that no selection bias exist in contrast to selection criteria commonly defined in clinical trial protocols. Data of this unselected population complete therefore data and experiences from clinical trials cited above. Patients received Ukrain in a high dose of 3x20mg i.v./week for 3 months. Both, total dose and response were higher than those reported in other publications.

"... evaluation criteria ...".

Of the 28 patients treated with Ukrain in 24 cases (85.71%) partial remission was achieved, details on the evaluation are not given in the publication; only 4 patients (14.29%) did not respond to treatment. On the other hand, mean survival of the patients treated with Ukrain was 784 days (26.13 months) after the beginning of Ukrain administration and 839 days (27.97 months) after diagnosing of inoperable form of pancreatic adenocarcinoma. This is an enormous progression in comparison to the survival known from literature and cited by EMEA (*... more than 80% of the patients die from disease within one year after diagnose ... the overall 5-year survival rate is less than 5%. Nonmetastatic, locally advanced disease is associated with an average survival of 6-10 months. Median survival for patients with metastatic cancer is 3-6 months*").

Now Pharm concludes that the EMEA opinion is incorrect as at least 21/28 patients were already in a very advanced stage and resistant to other chemotherapies; EMEA did not comment at all on the benefit of a considerable prolongation of survival.

Ad study: Gansauge et al, 2007 (p10/18):

The Gansauge et al. (2007, in press) study, which is an adjuvant trial in operable patients, is a single-arm case series study (with Gemcitabine plus Ukrain), and moreover there is a lack of a placebo group (which would have been necessary since there is no authorised drug for the adjuvant therapy of pancreatic cancer). Thus it is not possible to discriminate the effect of Ukrain from that of gemcitabine, or to establish if any effect of the treatment is present at all, as the only comparison is with historical data. It must be added that all patients in this study had tumour-free resection margins at surgery, and thus constituted a highly preselected group with a better prognosis in the first place.

"it is not possible to discriminate the effect of Ukrain from that of gemcitabine, or to establish if any effect of the treatment is present at all ..."

This publication provides additional data on the benefit of a combined, adjuvant treatment with Ukrain + gemcitabine: The relapse-free survival time was 21.7 months. The actuarial survival rates were 86.7% after one year, 76.6% after two years, 46.7% after three years and 23.3% after five years. The median survival time according to Kaplan-Meier regression analysis was 33.8 months. Again, this publication supports the efficacy (and safety) of the use of Ukrain combined with gemcitabine as it demonstrates a considerable prolongation of survival compared to what is known from literature.

Now Pharm concludes that again a clinical important endpoint such as survival has not been considered for the judgement by the EMEA expert. The EMEA opinion did also not comment at all on the excellent tolerance; grade II toxicity occurred in only 53%; no grade III or IV toxicity was observed. It is accepted that this population had a better prognosis. This conflicts however with an other comment of EMEA later on, were EMEA merges results from the combined treatment with those of Ukrain mono-therapy and where the prolonged overall survival is taken as an argument for assuming putative unreliable, biased results.

"Prof. Hans Winkler (EMEA/COMP Expert) also expressed concern about the reproducibility of clinical data due to several methodological issues": (p10/18)

Regarding the Aschhoff et al. study (2003), the results can not be evaluated, e. g. there were no control groups and there is no methodical description how tumour shrinkage was determined. The Gansauge et al. (2002) study has been severely criticised by the German Medical Association (Arzneiverordnung in der Praxis-Ausgabe 2/2002, p.9); the study was not blinded, therefore results on quality of life and tumour regression are not reliable. Furthermore, for the tumour marker response (Ca19.9), no significant differences between the three groups were observed. Also, randomisation apparently did not work well, since there were difference among the groups for sex and age: particularly worrying was the fact that the Ukrain groups included younger patients (lowest age: 22 year and 40 versus 53 in the gemcitabine group). Patients in the Ukrain group also had a history of more chemotherapy and radiochemotherapy. For all these reasons, the differences seen in survival time may be explained by methodical irregularities.

Ad: Aschhhoff 2003:

Prof. Winkler does not consider the fact that the publication (Aschhoff 2003, no co-authors!) focuses on overall survival which is an unbiased endpoint, not influenced from tumour size or metastases assessments. He distorts the publication to "tumour shrinking" which is obviously not the primary goal of the author. Dr Aschhoff. At this stage of an application for Orphan Drug Status it is not necessary to PROVE superiority but to demonstrate that there are reasonable grounds for such an assumption.

Ad: Gansauge et al., 2003:

Prof Winkler cites the article „Phase-II-Studie zur Behandlung des fortgeschrittenen, inoperablen Pankreaskarzinoms mit Ukrain" published in the journal „AVP Arzneiverordnung in der Praxis, Ausgabe 2, July 2002, as an opinion of the German chamber of physicians (http://www.akdae.de/25/Archiv/200202.pdf). It is worth to note however, that this article considered as so important to merit a reference by Prof. Winkler is anonymous; it is an unusual and un-academic procedure that – in contrast to other articles of the same journal – no author is stated. It could be Prof. Winkler himself or any other person that has reasons to remain anonymous. Strange enough, the article refers to another (negative) article (Arzneimittelbrief, Ausgabe 05, 2002) where again no author is stated.

Now Pharm considers therefore this opinion as biased and not reliable. It is also noteworthy that surrogates such as tumour marker CA19.9 (which are considered as secondary to clinical endpoints) are discussed by EMEA but not hard facts such as a significant prolongation of overall survival; criticism focuses on: "*that the study was not blinded, results on quality of life and tumour regression are not reliable*". As Prof. Winkler does not even mention the (positive) survival data, it can be concluded that the expert considers surrogate endpoints such as tumour markers and quality of life as clinically more reliable (or more important) than hard clinical endpoints. This is in contrast to the common medical opinion. A further observation is worth to be noted as well: Arguments against Ukrain are exactly the same as those provided by Prof. Winkler already years before.

Now Pharm considers quality of life and tumour response being secondary to overall survival.

Prof. Winkler explains the statistically significant superiority of Ukrain as well as of the combination of Ukrain + Gemcitabine by "*methodical irregularities*" and provides as "proofs" "*differences for sex and age*". Neither sex nor age are prognostic factors known to influence the course of pancreas carcinoma. On the other hand, with relatively small groups it is a common statistical finding that imbalances in at least one patient characteristic can be observed despite of correct randomisation: It is stressed that in two of three groups the sex distribution is as expected with slightly more male than female patients, in the group receiving gemcitabine alone however, about three times more male patients have been included. The therapeutic results are nonetheless in line with expectations from literature (see below); this aspect has however neither been considered nor commented by Prof. Winkler.

On p.13/18, EMEA states, the "*median survival time is approximately 4-6 months*". On the next page it is stated that the "*overall European mean 1 year relative survival is 15% for pancreatic cancer*". With that in mind, the following two facts are demonstrated by the present publication of Gansauge et al. (2003):

(i) The median survival of the control group receiving Gemcitabine in this study is 5.2 months thus perfectly well within expectations (4-6m);

(ii) the 1 year survival of this control group is 13% which is also close to the figure given by EMEA (15%). Both results are therefore in line to what is known from the literature cited by EMEA and confirm the validity of the study.

If results are explained by Prof. Winkler as "*methodical irregularities*", he completely ignores that results in the control group fit perfectly well to current knowledge and demonstrate therefore internal validity of this study.

As age and range have been criticised by Prof. Winkler ("*particularly worrying was the fact that the Ukrain groups included younger patients*") both the mean age and ranges are given here again for the sake of objectivity:

Gemcitabine: 63.8 (53-79);

Ukrain 60.6 (40-80),

Ukrain + Gemcitabine 58.2 (22-74).

As can be seen, the mean age is well comparable despite of small groups and only one patient that received the combination was very young.

Prof. Winkler's description of this study gives a wrong, misleading and one-sided opinion. If Prof. Winkler believes that a lower age improves outcome in pancreatic cancer he should support this by respective references to the literature and explain how a single patient would influence the overall outcome to the point of invalidating the results.

In contrast to sex and age, patient's characteristics taken by Prof. Winkler to undermine the study, tumour stage is commonly accepted as prognostic factor. It is worth to mention that the group receiving the combination and that demonstrated the best therapeutic results had the poorest prognosis with 22/30 patients in stage 4b and also the highest rate of metastasis. In addition, the highest proportion of patients with an unsuccessful pre-treatment was also found in the "*Ukrain groups*"; unsuccessful pre-treatment is also commonly considered as factor of poor prognosis.

Last but not least Prof. Winkler takes the fact of a relatively large span of average survival from 8.1 to 33.8 months as an additional argument to prove "methodological faults" and to express "*concern about the reproducibility of clinical data*". Here Prof. Winkler clearly merges cheese with chalk: 8.1 months median survival is for Ukrain only (Gansauge, 2002) and 33.8 for the combination of Ukrain + Gemcitabine (Gansauge, 2007).

In contrast to the EMEA expert, Prof. Winkler, Now Pharm concludes: ALL publications demonstrated, independently and in a reproducible way, a considerable prolongation of survival compared to other treatments; if differences in terms of survival are discussed by an expert this should consider as a minimum the nature of treatment, dose, population/patient characteristics and other circumstances such as duration of treatment.

Differences in patient characteristics occurred but Now Pharm concludes that such differences would certainly not favour the groups receiving Ukrain; even the contrary might be true. Prof Winkler failed to balance his speculations of a (putative) influence of sex and age on the outcome against other well known prognostic factors that can negatively influence treatment effects.

Ad: Zemskov et al., 2002:

In the study by Zemskov et al. (2000), randomisation apparently did not yield comparable groups, since men represented 81% in the Ukrain and only 47.6% in the control group; but on the other hand, which appears surprising, all the clinical parameters seemed to match extremely well for such small groups of patients. The survival rates of the Zemskov study showed remarkable results: in the control group more than 90% of patients had died within one year, compared to 24% in the Ukrain group; however, no further data concerning tumour growth, development of metastases etc, were presented. As data presented in a Journal are necessarily limited, it seems essential to obtain the original study protocol to evaluate this study. Finally, for the (as yet unpublished) Gansauge et al. (2007) study, the absence of a control group and the small size of the investigated group makes it difficult to reach a reliable conclusion.

"... randomisation apparently did not yield comparable groups ..."

Imbalances between groups in the study of **Zemskov et al.** (2002) may be explained as already outlined before; in this study, groups were even smaller with 21 patients per group. Again, the group receiving Ukrain had a higher percentage of patients with tumour stage 4b (33%) than the control group (24%); the Ukrain group had also more patients with metastasis (e.g., liver metastases, 23.8% vs. 14.3%). If imbalances are assumed to have influenced the overall survival / outcome data, this should clearly not distort treatment results in favour of Ukrain, on the contrary. Properties of the groups do therefore not support the statement of Prof Winkler

"*surprising, all the clinical parameters seemed to match extremely well for such small groups*". Such a statement distorts the facts, is misleading and could be easily misinterpreted as assuming manipulation.

Median and one year survival in the control group is again in an order that can be expected from the literature (6.4 months and 9.5% resp.). Similar to the study of Gansauge et al. (2002) this clearly demonstrates therefore internal validity of the study.

Now Pharm concludes that criticism by Prof Winkler is not objective: Concerning the publication by Dr Aschhoff as well as of Gansauge (2002) he does not consider overall survival; as to Gansauge et al., (2002) he takes sex and age as factors influencing the results; this is wrong as both factors have never been reported to influence the outcome in pancreas carcinoma treatment; imbalances in the study of Zemskov would suggest a less favourable outcome of patients receiving Ukrain, however the contrary was observed. Prof. Winkler provides never pros and cons in his assessments; he always arguments against Ukrain and distorts facts to discredit Ukrain. His opinion is therefore imbalanced and biased.

Now Pharm stresses further that Prof Winkler is not an expert in oncology.

III Criteria for orphan designation (p11/18)

1. Prevalence of the condition

Medical plausibility

Safety and tolerance of Ukrain is correctly summarised.

> Prof. Hans Winkler (EMEA/COMP Expert) also expressed doubts on the claimed greater cytotoxicity of Ukrain for cancer cells than for normal cells, based on the reported study by Panzer A et al. (2000), thus finding difficult to accept the Sponsor's claim that the concentration at which toxic effects are seen in healthy cells is more than 100 times higher than that lethal for all cancer cell lines.

See comments of Now Pharm on page 3.

> Four clinical studies were done in altogether 190 patients diagnosed with pancreatic cancer, claiming a substantial effect on survival for patients treated with Ukrain. However, the two allegedly randomised studies had multiple imbalance issues, which seriously impair the possibility of a clear interpretation of the results. The lack of the full protocol and results, repeatedly requested by EMEA to the Sponsor in this and in previous occasions but not provided, prevents an objective evaluation of the results. The two other studies, as reported in the previous comment, also present multiple methodological problems.

"... studies had multiple imbalance issues ... present multiple methodological problems"

This has already been discussed before. Statistically, the risk for imbalances between groups increase with the number of baseline characteristics compared and are inversely proportional to the number of patients per group. Age and sex are no factors known to influence treatment outcome in pancreatic cancer; double blind clinical trials are not always possible in oncology. In no case EMEA balances criticism against hard facts such as survival data but concentrates on secondary aspects such as tumour markers, or quality of life that are much more prone to vary and to be less conclusive for a clinical prognosis. Now Pharm cannot detect any efforts for an objective evaluation. On one hand, EMEA criticises the relatively large span of survival which was 33.8 months for the adjuvant study of Gansauge et al., (2007); on the other hand, EMEA considers this patient group with "*tumour-free resection margins*" and that received an adjuvant therapy with Ukrain combined with gemcitabine as "*highly preselected group with a better*

prognosis in the first place" (p11/18). Obviously, these two positions of EMEA conflict with each other and also with the fact that data of Ukrain monotherapy are mixed up with data of the combined treatment with gemcitabine.

In the eyes of Now Pharm this confirms the position of the sponsor that differences in survival may be explained by differences in patients and treatments (and not by "*multiple methodological problems*"). In no single case imbalances are such that they can influence the outcome in favour for Ukrain-treated patients.

Other statements are simply wrong (e.g.: concerning Zemskov et al., 2002: "*patients ... were given a choice between placebo and active treatment (Ukrain); this is likely to introduce selection bias and undermine the external validity of the results*"), or that "*no statistical comparison was performed between the two groups ... being only descriptive results*" (p.10/18), when in fact the publication gives Kaplan-Meier survival curves and states that a log rank test was performed.

Other comments of EMEA are surprising for (independent) EMEA experts: "... *when other researchers tried to investigate Ukrain in a phase II clinical trial ... they reported to have been unable to obtain the drug*" (p12/18).

Any drug that has received marketing authorisation can be used freely by physicians; it can be bought and imported by any international pharmacy. It must remain the right of the Sponsor to decide whether he is willing to provide the drug free of charge and to invest his money in a particular protocol/study or not.

2. Seriousness of the condition

No comments.

3. Currently available methods for diagnosis, prevention or treatment of the condition

Now Pharm stresses that Ukrain fulfils the requirement of Reg.847/2000 of 27apr2000, Art.2(3) "*that the medicinal product will be of significant benefit to those affected by that condition*".

4. Significant benefit

> Comparative pharmacodynamic studies in vitro and/or in vivo with the current authorised treatments of pancreatic cancer are not described in the sponsor's application.

"The sponsor did not initially submit a claim of significant benefit over erlotinib". (p15/18)

Erlotinib/Tarceva received Marketing Authorisation very recently, on 24jan07 only whereas the application was submitted on 06feb07. A direct comparison was not possible, most of the original clinical data are inaccessible.

The following results should be well known to EMEA:

Use in advanced pancreatic cancer (Gansauge et al, 2002; Moore et al, 2005).

	Ukrain/Ukrain + gemcitabine	**Erlotinib + gemcitabine**
Patients	60 (with) + 30 (without)	261 (with) + 260 (without)
Placebo controlled	no	yes
Concomitant treatment	gemcitabine	gemcitabine
First line/adjuvant therapy	first line and adjuvant	first line
Survival		
Median	7.9 mo/10.4 mo	6.4 mo
1-year	29%/32%	23.8%
Progression-free		3.8 mo
Response (CR+PR)	10%/21%	8.6%
Response duration		23.9 wk, median
Toxicity		
Pulmonary	-	interstitial lung disease, 2.5%
Heart	-	Infarction/ischemia, 2.3% (1 death)
Cerebrovascular	-	2.3% (1 death)
Tumor bleeding	7%/7%	-
Skin rash	-	69% (grade 3/4 – 5%)
Diarrhea	25%/21%	48% (grade 3/4 – 5%)
Fatigue	-	73% (grade 3/4 - 16%)
Nausea	22%/27%	60% (grade 3/4 – 7%)
Constipation	10%/9%	35%
Fever	42%/34%	39%
Weight loss	-	39% (grade 3/4 - 2%)
Deep venous thrombosis	-	3.9%
Hematological	43%/85%	

Ad 15/18:

> Given the lack of preclinical comparative data, and the multiple methodological issues of the single clinical comparative study performed with the use of currently authorised products, it is difficult to accept the claim of significant benefit over the currently authorised products.

Now Pharm refers to the Reg.847/2000 of 27apr2000, Art.2(4) according to which a sponsor can apply "*at any stage of the development of the medicinal product*". Now Pharm presented clinical data that allow indirect comparison with erlotinib. These data are suggestive for a considerable clinical benefit over erlotinib.

> The claim of significant benefit over the currently available treatment methods, in particular over gemcitabine and over erlotinib is not sufficiently supported by the currently available evidence, given the conflicting preclinical evidence, the methodological issues, and the lack of reproducibility that have been reported in the literature and commented in the previous sections.

It is the opinion of Now Pharm that there are no methodological issues that justify a conclusion of "*lack of reproducibility*".

Safety of Ukrain:

The EMEA/COMP Expert Prof. Winkler expressed doubts regarding the claim of improved safety reported by the Sponsor:

A hepatotoxic effect of these alkoloids has been established. Benninger et al. (Gastroenterol. 117, 1234, 1999, see also Deutsche Apothekerzeitung 142, 32 2002) reported 10 cases of cholestatic hepatitis. Panzer et al. (Cancer letters 150, 85, 2000 c) state and quote literature: "Chelidonine has long been found to have side-effects, in doses which are tumorolytic, too severe to justify its use in clinical medicine."

The claim by the company for Ukrain that is has little side effects, and no hepatotoxicity, is therefore difficult to accept.

In the Investigator's Brochure a 6 month study on rats (i.m.) is presented. In this study "a minimal to mild hepatocellular degeneration at all doses" was reported. As an explanation for the claim of a low toxicity of Ukrain Panzer et al. (2000) suggest: "The lack of side-effects found in vivo may be due to the lack of therapeutically effective dosages being administered".

In conclusion, the Sponsor has not supplied sufficient argumentation to claim a potential significant benefit of Chelidonii radix special liquid extract over currently authorised treatments for treatment of pancreatic cancer, neither through better efficacy, better safety, or a significant contribution to patient care.

It is obvious that Prof. Winkler is merging cheese with chalk: Ukrain is a unique liquid extract of chelidonium majus; this unique nature has been recognised by EMEA. How can a drug (or a single alkaloid, chelidonine) that is differently prepared and that is not water-soluble and that can be administered exclusively by oral route, be compared 1:1 with an extract that can be injected intravenously and intramuscularly? The process of absorption from gut, possible effects such as a first pass-effect, composition of the various alkaloids, chemical form of alkaloids which may also induce differences in metabolisation, etc. are completely neglected by the EMEA expert.

It is reminded that on page 6/18 EMEA concludes that "*no free Thio-TEPA or aziridine ring compounds can be detected in NSC 631570. Ukrain is therefore definitively different from the starting materials*". EMEA accepts therefore the opinion of the sponsor on page 8/18; "*the previously findings that the drug possesses other pharmacological properties compared with the start components for its synthesis seem confirmed*".

On one hand, Prof Winkler tries to construct a hepatotoxicity for Ukrain that has not been observed to a relevant extent in man despite that over 800 patients have been treated in monotherapy as can be demonstrated by Nowicky Pharma. On the other hand Prof Winkler cites (see below) a publication in order to explain the lack of side effects with a lack of efficacy – a contradiction and nonsense in the eyes of Nowicky Pharma. Not only that pancreas carcinoma patients demonstrate frequently abnormal liver function parameters, a significant toxic reaction due to Ukrain has not been observed. Furthermore, patients suffering from hepatitis C have been successfully treated with Ukrain (HCV-RNA, PCR testing) without any serious adverse reactions or adverse influence on liver or other organ function parameters.

In the study of Zemskov et al. (2002) the authors were monitoring the parameters of cholestasis (as known parameters of liver toxicity) in pancreatic cancer patients (AST, ALT, GGT, bilirubin) and also in many other patients in the same clinic after registration of Ukrain in the Ukraine. It is surprising to see that Prof. Winkler as an expert in medicine did not take note of these data regarding toxicity (Zemskov et al. 2002). The Table 3 (Zemskov et al. 2002) demonstrates that in the group receiving Ukrain as well as in the control group (supportive treatment) only low, insignificant toxicity was observed (Grade 1, after Classification of World Health Organization, was observed in only 9,5% of the Ukrain group and in 4,8% of the patients of the control group). Summarised, only in 9,5% patients liver toxicity Grade 1 was observed but no toxicity Grade II or III or IV. Compared with conventional chemotherapy the liver toxicity of Ukrain is rarely

observed and extremely low. In contrast, in all studies with erlotinib/tarceva the liver toxicity was much higher.

Table 3. WHO Grades Laboratory Toxicity
(Values are given as percentage of patients), Zemskov et al, 2002.

WHO Grades	Group	Segmented neutrophils	WBCs	Hemoglobin	AST	ALT
0	Ukrain	100.0	100.0	95.2	90.5	90.5
	Control	95.2	95.2	76.2	80.9	76.2
1	Ukrain	0	0	4.8	9.5	9.5
	Control	0	4.8	4.8	0	4.8
2	Ukrain	0	0	0	0	0
	Control	4.8	0	9.5	9.5	19.0
3	Ukrain	0	0	0	0	0
	Control	0	0	9.5	9.5	0
4	Ukrain	0	0	0	0	0
	Control	0	0	0	0	0

WBCs-white blood cells. AST-aspartate transaminase, ALT-alanine transaminase

This safety aspect should be compared to the situation with erlotinib: Recently, a case of acute drug-induced hepatotoxicity secondary to erlotinib was reported; in general, grade 3 and 4 elevations in transaminases are uncommon after single agent gefitinib and erlotinib.
In the phase I study by Hidalgo *et al.*, grade 1 hyperbilirubinemia occurred in patients with advanced solid tumors which was not associated with elevated hepatic transaminases (summarized in Ramanarayanan and Scarpace, 2007). Among 42 patients with advanced biliary malignancies treated with erlotinib, grade 3 toxicity was noted in one patient (0.2%) and one of the 38 patients with hepatocellular carcinoma had developed grade 3 liver enzyme elevation at 150 mg/day dose level. Recent phase III study of gemcitabine with erlotinib (100 mg/day) or placebo in patients with advanced pancreatic malignancies, showed no statistically significant elevation in grade 3 liver toxicity with addition of erlotinib, although 10% grade 3 elevation of aminotransferases were reported in both the groups (summarized in Ramanarayanan and Scarpace, 2007).

1. Ramanarayanan J, , Scarpace SL Acute Drug Induced Hepatitis Due to Erlotinib JOP. J Pancreas) 2007; 8(1):39-43.
2. Liu W, Makrauer FL, Qamar AA, Jänne PA, Odze RD.
Fulminant Hepatic Failure Secondary to Erlotinib. Clin Gastroenterol Hepatol. 2007 Jul 9

Prof. Winkler had already cited Panzer et al., 2000 ("*the lack of side-effects found in vivo may be due to the lack of therapeutically effective dosages being administered*") during the oral presentation end of May. In view of the preclinical and clinical results demonstrating efficacy of Ukrain, such a comment does not only lack of any objectivity but is inappropriate for an EMEA expert in the eyes of Nowicky Pharma. It is also reminded that Ukrain can be injected intramuscularly; in contrast, any other chemotherapeutic agent would induce sever necroses.

5. Demonstration of insufficient return on investments

Not applicable.

6. Overall conclusion

However, based on the pre-clinical evidence, the preliminary clinical data, the justifications provided, the opinion of the COMP experts, and the published literature, the assumption that Chelidonii radix special liquid extract could be of potential significant benefit for patients affected by the condition does not appear justified.

Now Pharm disagrees with the conclusion of EMEA.

Now Pharm concludes that EMEA efficacy evaluations have been done with two sorts of measures when compared with Erlotinib:

Erlotinib has demonstrated a gain in overall survival of ONLY 0.5 months (!!) compared to placebo, in contrast to Ukrain, that has repeatedly and consistently demonstrated a clinically and statistically significant prolongation of survival in the order of several months in independent publications; in addition, over 70% of patients treated with erlotinib show exanthema whereas Ukrain is well tolerated (see citation below: "*lack of side effects*").

If EMEA considers treatment successes described in the studies provided as a matter of mere chance one would expect that results are scattered around the known figures of "*overall European mean 1 year relative survival for pancreatic cancer* ". However, the contrary is observed: (i) All three publications consistently demonstrate a considerably longer survival; (ii) prolongation of survival is not by a few percent or about 2 weeks but by in a striking order of magnitude of several hundred percent. A further, 4th study that has just been submitted for publication supports these data (Gansauge et al., 2007). Such magnitudes are extremely unlikely to occur repeatedly, just by mere chance and in different studies.

In contrast to EMEA, Now Pharm considers a reproducible prolongation of survival by several months as well as an improved safety/tolerance as a significant progress in treatment of pancreas carcinoma patients and as a significant therapeutic benefit.

Similar to the evaluation concerning the claim of improved efficacy also the assessment of **improved safety** by the EMEA expert Prof Winkler is misleading and inconclusive: Prof Winkler cites, for proving his arguments, cases of cholestatic hepatitis observed after ORAL intake of UNPROCESSED, commercial products containing Chelidonium majus alkaloids. After oral intake of such products, substances are absorbed by the gut mucosa and transported in concentrated form by the blood directly to the liver via the portal venous blood; metabolites might be formed in high concentration due to a possible first pass effect. The liver is therefore the first organ that these substances pass before entering the general circulation and before being diluted by the blood stream. None of these aspects has been discussed by Prof. Winkler.

Ukrain cannot be compared to these products for the reasons explained already before: (i) Ukrain is injected intravenously, diluted by the blood and reaches all organs primarily by the general, arterial blood stream and not by the portal vein. (ii) If one product is water-soluble, the other however not, it is quit obvious that chemical forms and biological properties of these products cannot be the same. (iii) The relative ratio and composition of alkaloids in Ukrain is different from the (unprocessed) oral Chelidonium majus products of which Prof. Winkler cites cases of adverse reactions. (iv) It is not clear to what extent individual alkaloid components of such oral Chelidonium majus products reach the liver; their concentrations could be much higher, their route of metabolisation may be different. Again, this aspect has not been critically discussed by the EMEA expert Prof Winkler. Differences to Ukrain can be assumed, thus explaining obvious differences in their safety profile. Nonetheless, Prof. Winkler maintains that Ukrain must have the same safety/tolerance profile as oral preparations of chelidonium majus. In addition, Prof. Winkler disregards that Ukrain has been given successfully to over 800 patients including those suffering from liver damages as a result of hepatitis C without any hepato-toxic effects.

Prof Winkler refers as further argument to a speculation of Panzer et al., (2000): "*The lack of side effects found in vivo may be due to the lack of therapeutically effective dosages being administered*". This is considered as unscientific statement, unsupported by the documents provided to EMEA; this demonstrates lack of objectivity as would however be a pre-requisite for an EMEA expert in the opinion of Nowicky Pharma.

In summary, judgements of EMEA, in particular of the EMEA expert Prof. Winkler, are not objective; many aspects in the publications provided have either been misinterpreted or disregarded. Now Pharm has grounds to assume that the EMEA expert, Prof. Winkler, has mainly influenced the negative decision of EMEA; Prof. Winkler is biased in his view of the results on clinical trials with Ukrain, both concerning efficacy as well as of safety. Prof. Winkler is also not an expert in oncology. None of his assessments is objective. Prof. Winkler maintains his personal, negative opinion forwarded already 5 years ago to the Austrian Health Authority, with exactly the same arguments despite of additional data; his argumentation, that "*methodological Irregularities*" could have distorted the results in favour of Ukrain and its combination is irrational and lacks any evidence.

Now Pharm believes that the documentation submitted fulfils the requirement of Reg.847/2000 of 27apr2000, Art.2(3) "*that the medicinal product will be of significant benefit to those affected by that condition*".