5.6.3.2.1 IV Study - Study 25506 - Nov 1992

Study 25506 was a pharmacokinetic study of intravenous administration of asenapine at four different doses, with each dose to be administered to two healthy male volunteers which was then to be followed by a pilot bioavailability study of 30 mg orally in the two volunteers who received the highest tolerated intravenous dose.

The study was stopped after the first two subjects due to asystole requiring external cardiac massage and atropine. Although attributed by the sponsor to a vasovagal effect, an external cardiologist deemed it a serious AE of asenapine affecting the conducting system of the heart, (see Figure 206 to Figure 211).

What is particularly worrisome is that this occurred at a dose of 0.7 mg shortly after a 30 minute infusion in a young healthy individual with no evidence of any cardiac disease. With an average absolute bioavailability of 33% (and up to 50%) this translates into a sublingual dose of 1.4 mg - 2.1 mg and is unlikely due to metabolites. Thus arrhythmias are a concern with clinical doses.

Figure 206 Text from IV Study 25506

This study was stopped after one of the two subjects collapsed in asystole. Prompt resuscitation resulted in the patient being asymptomatic 24 minutes after the initial collapse. Anxiety about the other subject's adverse event may have contributed to subject's 1/2(0.7mg) dizziness.

Figure 207 Text from IV Study 25506 (Continued)

Cardiac investigations - including a 24 hour Holter ECG, echocardiogram, exercise ECG and carotid sinus massage - revealed no cardiac pathology that may have predisposed to the event.

Org 5222 has alpha-blocking activity. It is possible that the drug aggravated hypotension (during sitting) and this precipitated an inappropriate vagal response in a vagotonic (athletic) subject. However, this does not adequately explain the persistence of the sinus arrest and the lack of response to lying supine.

Figure 208 Text from IV Study 25506 (Continued)

This study was stopped because subject 1/1(0.7mg) collapsed 45 minutes after the start of the 30-minute infusion, while having his sitting blood pressure measured. Before he collapsed he stated that he felt dizzy and unwell, then immediately fell back onto the bed. The ECG monitor showed asystole. The subject was shaken and made a transient verbal

Figure 209 Text from IV Study 25506 (Continued)

response. He had no pulse and was very pale. The foot of the bed was elevated. Cardiac massage commenced and after approximately five thrusts to the sternum, he made a transient verbal response: he asked what was happening. The cardiac massage, which lasted about 5 seconds, appeared to stimulate a nodal bradycardia before reverting to asystole. The subject again lost consciousness. The cardiac massage was repeated for another 5 seconds, with improvement in consciousness. The subject was continuously unconscious for not more than 30 seconds. However, severe bradycardia with intermittent nodal complexes and AV dissociation persisted until two doses of atropine (0.6mg i.v.) had been administered at 01 00 49 and 01 00 54. Haemaccel (one unit i.v.) was administered at 01 00 59. Oxygen was removed at 01 01 10. Sinus tachycardia resulted within seconds, the subject became normotensive and fully regained consciousness. Twenty-four minutes after the initial collapse, the subject was asymptomatic. Plasma electrolytes (Na, K, Ca and Mg) in the additional blood samples taken (see section 6.2) were normal. Subsequent cardiac investigations and cardiological opinion (see letter of 23 december 1991 in appendix 14) revealed no predisposing or post-event cardiac pathology. The cardiological investigations - a physical examination, 24-hour tape-recorded ECG, two-dimensional echocardiogram, treadmill exercise ECG, and carotid sinus massage - could not identify any cardiac abnormality.

Subject 1/2(0.7mg) had been dosed and began to feel dizzy before subject 1/1(0.7mg) collapsed. This adverse event was initially considered mild, but when he felt dizzy on standing - 30 minutes after dosing - it was considered to be of moderate severity. By that time subject 1/1(0.7mg) had collapsed.

Figure 210 Cardiologist's Report from IV Study 25506

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GJ/HS

23rd December 1991

Dr. Tim Mant,
Guy's Drug Research Unit,
6 Newcomen Street,
London, SE1 1YR

Dear Tim,

Re: (b) (4) 001 026 5222 I.V. 57-DY

Thank you for asking me to assess this 27 year old chap who had an unfortunate event as a result of participating in a normal volunteer study. I've looked at the sequence of ECGs and there's no doubt that he became asystolic and as you pointed out you had to perform cardiac massage to sustain an output. It is interesting looking at the sequence of events because in the first instance there's obviously sinus arrest but then as he recovers there's evidence of AV conduction abnormalities also with a gradual return back to normal sinus rhythm.

With regard to him, he's always been fit, well and very active and though he currently works as a casino manager, in the past he's had a healthy lifestyle being an ex-marathon runner and still keeping reasonably fit. He's single, a non smoker, only drinks alcohol at the weekends. He's never been ill apart from a road traffic accident five years ago when he had some cervical spine damage.

EXAMINATION

He looks fit and well. JVP not raised, sinus rhythm, blood pressure 110/80. There were no murmurs, there were two heart sounds, there was no suggestion of heart failure and the lungs were normal and clear.

INVESTIGATIONS

24 Hour Tape Recorded ECG: Normal sinus rhythm with respiratory variation.

2D Echocardiogram: Normal.

Treadmill Exercise ECG: He managed an above average 15 minutes going to his maximal heart rate of 194 beats per minute. There were no arrhythmias and no ischaemic changes.

Carotid Sinus Massage: Massage of both the right and left carotids did not induce any significant bradycardia.

OPINION

First of all I cannot identify any cardiac problem in (b) (4) and I've reassured him that there's no evidence of any cardiovascular disease.

Figure 211 Cardiologist's Report from IV Study 25506 (Continued)

Conclusion

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

Graham Jackson
CONSULTANT CARDIOLOGIST

5.6.3.2.2 Multiple Rising Oral Dose Study - Study 25501 – June 1993

Study 25501 was a multiple rising dose study to examine the pharmacokinetics in 12 young, healthy, male volunteers using Org 5222 both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily orally).

One subject had asystole for 8.7 seconds with a junctional escape rhythm. Even though this was a single oral dose of 30 mg and the asenapine exposures was low compared to what is typically seen with sublingual dosing, the N-desmethylasenapine exposures were similar to those seen in multiple dose studies with sublingual dosing, (see Table 191). It's noteworthy that the sponsor did not include the data range for the most important study in any of the summary tables for the pharmacokinetics. In addition, the study durations were short, (5 and 6 days), and with a half-life in some cases of a couple of days and likely time dependent kinetics for desmethyl-asenapine the true exposures at steady-state are likely underestimated.

Figure 212 Text from PO MRD Study 25501

A previous study showed that multiple dosing with Org 5222 15mg twice daily for six or more days increased serum alanine aminotransferase and aspartate aminotransferase in three out of six healthy, male subjects.

Sponsor refers to first case as "cardiac arrest"

Figure 213 Text from PO MRD Study 25501 (Continued)

In a previous study at GDRU, intravenous Org 5222 was associated with a cardiac arrest.

After oral administration the bioavailability of Org 5222 is minimal in most subjects.

Figure 214 Conclusions from PO MRD Study 25501

SUMMARY - CONCLUSIONS

After the single, oral dose of Org 5222 to the six subjects of the first group, the study was terminated due to a serious adverse event in one subject.
Two hours, 25 minutes post dosing the subject suffered an 8.7 second asystolic episode followed by junctional escape rhythm until sinus rhythm was restored. A subsequent 24-hour ECG was normal and no abnormalities were detected on echo cardiography. There were no other serious events. In general, subject's supine blood pressure and pulse rate showed only the random fluctuations expected. Apart from the subject who suffered the asystolic episode, there were no clinically significant changes in the 12-lead-ECG recordings following Org 5222 in the 5 other subjects. There were no clinically significant abnormalities on either physical examination, Multistix® urinalysis, clinical chemistry or haematology.

Figure 215 PK from PO MRD Study 25501

Pharmacokinetics

Blood samples were taken at pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 24, 36 and 48 hours after drug administration. Mean values (n=6) for the pharmacokinetic parameters are summarized in the table below.

Summary of the pharmacokinetic data

Parameter	Org 5222				Org 30526			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
C_{max} (pg.ml^{-1})	390	186	144	682	3813	617	3330	4930
t_{max} (h)	1.50	0.89	0.50	3.00	2.86	1.13	1.50	4.00
$AUC_{0-\infty}$ (pg.ml^{-1}.h)	3701	1146	1937	4988	44119	10804	29824	58452
$t_{1/2}$ (h)	7.87	1.96	6.27	11.13	10.54	1.50	8.54	12.11

SD = Standard Deviation; Min. = Minimal value; Max. = Maximal value

Conclusions

The Org 30526 plasma levels were considerably higher than those of Org 5222. The elimination half-life of Org 30526 was slightly, but significantly longer than the half-life of Org 5222. A single oral dose of 30 mg Org 5222 in healthy male subjects was not well tolerated as it produced a serious adverse event in one of the six subjects treated.

Table 191 Comparison of Selected Pharmacokinetic Metrics for Study 22501 and Multiple Dose PK Studies.

Metric	Cmax (ng/mL)			AUCτ[b] (ng/ml x hr^{-1})		
Study	Study 22501	25542	41012	Study 22501	25542	41012
Dosage Regimen	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days
Asenapine	0.39 ± 0.18 0.14 – 0.68	5.57±2.36 0.94 – 8.81	8.84 2.17 - 15.5	3.7±1.2 1.9 - 5.0	28.2±16.0 6.0 – 53.5	37.3 16.5 - 58.1
Desmethyl-Asenapine	3.8 ± 0.62 3.33 - 4.93	3.14±1.2 0.48 – **5.16**	1.33 1.23 - 1.42	44.1±10.8 29.8 – 58.4	31.8±14.3 4.7 – **53.8**	12.7 11.0 - 14.4

a Text in red was not reported in clinical study report or in any summary tables, had to be extracted from raw data
b For single dose study AUC = AUCinf

5.6.3.2.3 Initial SL Single Rising Dose Study - Study 25509

The following is the background safety information from the initial sublingual dose study with a dose range of 10 - 100 mcg, (see Figure 216 and Figure 217).

What noteworthy about this summary is that it is precludes chronic oral dosing of greater than 4 mg / day due to safety reasons, which is equivalent to 8 – 12 mg /day administered sublingually. In addition it indicates that subjects with high Cmax's have serious AEs, and that interindividual variability results in greater risk in some individuals. Although it's reported that high Cmax's are potentially related to serious AEs individual Cmax's from these studies are not reported and it's unclear if this is related to asenapine or desmethyl-asenapine concentrations.

This was another study that this reviewer was told not to review as it did not include the proposed clinical dose range.

Figure 216 Text from SL SRD Study 25509

1.2 Summary of relevant safety data

Org SL94 appears to be safe in endocrinological, biochemical and haematological terms, however single high doses of Org SL94 may induce cardiovascular adverse experiences in animals and humans.

Single dose i.v. administration of Org SL94 to rats at dose levels up to 21 mg/kg caused no mortalities but was associated with neurological symptoms. The i.v. toxicity studies in rats and dogs with daily administration for 2 weeks at dose levels up to 3 mg/kg caused no overt signs of toxicity. Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses.

In the initial Phase I studies in healthy male volunteers, single oral doses up to 30 mg Org SL94 did not cause any safety problems. In a two week multiple dose study oral doses up to 15 mg twice daily were administered. Time and dose dependent increases in ALT and AST serum levels were observed.

In two subsequent studies with healthy male volunteers, two serious adverse experiences (SAEs) were observed. The first SAE (cardiac arrhythmia - asystole) occurred 15 min after the i.v. infusion of 0.7 mg Org SL94 (given over 30 min), when the subject was asked to sit up. He required brief external cardiac massage and atropine and made a full

Figure 217 Text from SL SRD Study 25509 (Continued)

recovery. He was never unconscious for more than 30 seconds. The second SAE occurred 2 h 35 min after a single oral dose of 30 mg Org SL94 without an obvious precipitating factor. This subject collapsed whilst already sitting and recovered spontaneously. His ECG at the time of the collapse showed a prolonged sinus pause. The pharmacokinetic results revealed large inter-individual variation in oral Org SL94 plasma levels and relatively high C_{max} values were observed in the individuals exhibiting serious adverse events. However, in view of the limited data it is not possible to draw definite conclusions as to the quantitative relationship between C_{max} and the SAE. The oral bioavailability of Org SL94 was calculated to be approximately 1%.

Three Phase II studies have been conducted with orally administered Org SL94 in the treatment of schizophrenic patients. The results indicate that the highest dose applied (4 mg/day) may be considered the minimal effective dose. No safety problems were encountered.

From a safety point of view, chronic administration of doses higher than 4 mg/day is precluded for two reasons: 1) the risk of hepatotoxicity 2) due to the fact that low oral bioavailability predisposes to highly variable plasma levels, patients may be put at increased risk for cardiovascular adverse experiences.

5.6.3.2.4 Pivotal BE Study (b) (4)) - Study A7501015

The sponsor states that there were 12 serious AEs however other than indicating the number of AEs they are not identified in any way. In addition two subjects withdrew due to "hypotension" 2 withdrew consent and 2 for other reasons however they were not identified so even the hypotension cannot be verified.

In the background information the co-sponsor (Pfizer) identified the above cardiac arrhythmias as Neurally Mediated Reflex Bradycardia, (see Figure 218). It is inconceivable to this reviewer how the sponsor can make this statement.

Figure 218 Pfizer's Discussion of Previously Observed Cardiotoxicity – Study A7501015

In early trials, a total of 4 young healthy male volunteers experienced an untoward adverse experience identified as Neurally Mediated Reflex Bradycardia (NMRB) with sinuspause; ie, 1 subject after receiving 0.15 mg asenapine by the sublingual route, 1 after receiving placebo via the sublingual route, 1 after receiving 30 mg via the oral route, and one 45 minutes after receiving 0.7 mg/30 min asenapine intravenous. All occurred after the first dose and after postural challenge. This reflex is seen in 5%-10% of the general population and is benign and self-limiting. It occurs typically secondary to postural changes, younger age, and high vagal tone (low resting heart rate).