



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Digoxin-specific antibody fragment F(Ab) (Ovine)

Proprietary Product Name: DigiFab

Sponsor: Phebra Pty Ltd

First round report: 7 June 2013

Second round report: 13 September 2013

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

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List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse Event
AUC	Area under curve
AUMC	Area under the first-moment versus time curve
Az	Smallest disposition rate constant
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
CK	Creatine kinase
CRF	Case report form
CV	Coefficient of variation
Clast	Last measured concentration
Cl _{total}	Systemic clearance
Cl _{renal}	Renal clearance
Cl _{non-renal}	Non renal clearance
C _{max}	Maximum concentration
CFR	Code of Federal Regulations
CRF	Case Report Form
D	Dose in mg
DBP	Diastolic blood pressure
ECG	Electrocardiogram
Fab	Fragment antigen binding
GCP	Good Clinical Practice
GOT	Aspartate aminotransferase
GPT	Alanine aminotransferase
GT	Glutamyl transpeptidase

Abbreviation	Meaning
HASA	Human Anti-Sheep Antibody
Hr	H(s)
IC	Informed Consent
IgG	Immunoglobulin G
IRB	Institutional Review Board
Ke	Elimination rate constant
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LOQ	Limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume of erythrocytes
Min	minute(s)
MHRA	Medical and Healthcare products Regulatory Agency
MRT	Mean residence time
N	Number
NA	Not applicable
NS	Not significant
P	Probability
PD	Pharmacodynamic
PK	Pharmacokinetic
PTQ	PR interval x T score/QT c
PTT	Partial thromboplastin time
RIA	Radioimmunoassay
SBP	Systolic blood pressure

Abbreviation	Meaning
SD	Standard deviation
SEM	Standard error of the mean
SD	Standard Deviation
T	Time of infusion
$t_{1/2p}$	Terminal slope elimination half-life
$t_{1/2a}$	Distribution (a) half-life
Tmax	Time to maximum concentration
Vdss	Steady state volume of distribution
Vc	Volume of central compartment
WHO	World Health Organization

1. Clinical rationale

At present, the standard of care applied in the treatment of life-threatening digoxin, or digitalis poisoning in Australia is Digibind®. This is a product which is clinically interchangeable with DigiFab and is currently registered on the Australian Register of Therapeutic Goods and marketed by the sponsor, GlaxoSmithKline (GSK). [information redacted] Other measures to manage patients suffering from digoxin poisoning include administration of liquid charcoal, cholestyramine or magnesium sulphate, these all have limitations, either requiring administration within 30 minutes of overdose, a long administration time, or are purely for short term management of the cardiac symptoms. The introduction of DigiFab would be a valuable addition to the treatment options for this condition and would safeguard supply of a potentially life-saving product for the treatment of digoxin and digitoxin poisoning for the Australian population.

Many clinical studies have shown that binding of digoxin by Fab fragments promptly reduces the toxic activity of the drug (Smith, 1982; Antman, 1990; Wenger, 1985). Therefore, the clinical studies were designed to demonstrate primarily that DigiFab, when administered to patients who were experiencing digoxin toxicity, would reduce serum free digoxin levels to below a clinically meaningful concentration (<0.5 ng/ml). The studies also evaluated the ability of DigiFab to neutralise the toxic effects of digoxin and reverse potentially life-threatening toxic manifestations of digoxin overdose and toxicity. Due to the well understood safety and mechanism of action of Digibind and similarity of DigiFab, it was considered relevant to conduct a clinical programme to show that DigiFab binds and inactivates digoxin in healthy subjects in an equivalent manner to Digibind and produces the same clinical benefit in intoxicated patients.

Comments: It is important to note that authorisation of DigiFab is not being sought on a biosimilar basis. However, it is acknowledged that this comparison of DigiFab with already approved Digibind would still be relevant to the demonstration of efficacy for DigiFab. Furthermore, evidence for efficacy of DigiFab is provided from the clinical studies in terms of binding of DigiFab to digoxin (measured as free and total digoxin

concentrations) and clinical evidence of concomitant loss of toxic effects of digoxin (ECG changes, clinical sequelae)

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Three clinical studies, TAb007-01, TAb007-02 and PR007-CLN-rpt-003, which are the only studies to have been specifically performed on DigiFab® worldwide. Studies TAb007-01 and TAb007-02 were designed to compare DigiFab® (known as DigiTAB at the time of these studies) to Digibind in a clinical development program [information redacted]. Study PR007-CLNrpt- 003, a retrospective study on the use of DigiFab® in the US, was initiated at the request of the Medical and Healthcare products Regulatory Agency (MHRA) to provide additional evidence of efficacy.

DigiFab was originally developed in the US; therefore, some documents in the enclosed dossier refer to the active ingredient by its US approved name of “Digoxin Immune Fab (Ovine)” instead of the Australia Approved name “Digoxin-specific antibody fragment f(Ab) (Ovine)”. The sponsors have assured the TGA that both these names refer to the same active ingredient. It is important to note that DigiFab® was initially called DigiTAB and both these terms have been used interchangeably in the CSRs in the submitted dossier and throughout this evaluation report.

Comments: Life-threatening digoxin toxicity is not common and, as such, DigiFab has been designated an orphan medicinal product in Australia whereby the prevalence of the condition must be less than 2000 patients. The rarity of the condition, coupled with the indicated use in a hospital emergency setting, meant that a conventionally designed clinical trial programme was not appropriate, or even possible for DigiFab. The nature of the condition severely restricted the ability to recruit adequate numbers of subjects in order to pursue formal randomised, controlled trials. It is acknowledged that the clinical data set is limited compared with the current expectations for a standalone marketing authorisation application but this is a result of the emergency nature and the prevalence of the condition. The sponsor does not intend to conduct further clinical studies of DigiFab.

2.2. Paediatric data

The submission did not include paediatric data. Specific studies in paediatric patients have not been conducted and no paediatric patients were enrolled in the clinical studies of DigiFab®. A similar digoxin ovine Fab product, Digibind®, has been used successfully to treat infants. As with all drugs, the use of DigiFab® in infants and children should be based on careful consideration of the benefits compared with the potential risks.

2.3. Good clinical practice

All studies were conducted in accordance with the protocol and Good Clinical Practices (GCP) including the archiving of patient records and informed consent documents.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

There were 2 clinical pharmacology studies (**TA007-02** and **TA007-01**), both provided PK and PD data.

Table 1 shows the studies relating to each PK topic.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	TA007-02
	- Multi-dose	NA
	Bioequivalence† - Single dose	NA
	- Multi-dose	NA
	Food effect	NA
PK in special populations	Target population § - Single dose	TA007-01
	- Multi-dose	NA
	Hepatic impairment	NA
	Renal impairment	Literature only
	Neonates/infants/children/adolescents	NA
	Elderly	NA
Genetic/gender-related PK	Males vs. females	Not evaluated
	Other genetic variables	NA
PK interactions		Not evaluated
Population PK analyses	Healthy subjects	NA
	Target population	NA
	Other	NA

NA- Not applicable. vs=versus

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

As DigiFab is an intravenously administered product, biopharmaceutic studies were not performed.

Serum and urine were analysed for free and total digoxin at the University of Massachusetts Drug Concentration Laboratory, a College of American Pathologists (CAP) accredited laboratory division within the Department of Hospital Laboratories at the University of Massachusetts Medical Center. In order to isolate free digoxin, serum and urine samples were filtered using a Centrifree micropartition device (Amicon, Inc. Beverly, MA). Free digoxin was then quantified using the OnLine Test Kit for Digoxin (Roche Diagnostic Systems, Somerville, NJ) on a Roche Cobas FARA Instrument. This test is a homogeneous, competitive binding immunoassay. In order to quantify total digoxin, serum and urine specimens were boiled in order to release digoxin from Fab. Subsequently, digoxin concentrations were measured using the same immunoassay method as for free digoxin. Pharmacokinetic parameters for Fab (DigiFab and Digibind) were determined using a non-compartmental pharmacokinetic model

3.3. Pharmacokinetics in healthy subjects

3.3.1. Absorption

3.3.1.1. *Sites and mechanisms of absorption*

See section **Excretion** below.

3.3.2. Bioavailability

3.3.2.1. *Absolute bioavailability*

DigiFab is administered intravenously.

3.3.2.2. *Bioavailability relative to an oral solution or micronised suspension*

Not applicable.

3.3.2.3. *Bioequivalence of clinical trial and market formulations*

Not applicable.

3.3.2.4. *Bioequivalence of different dosage forms and strengths*

Not applicable.

3.3.2.5. *Bioequivalence to relevant registered products*

An open-label, randomised, parallel group, single centre trial (**Study TAb007-02**) in 16 healthy, male and female volunteers was conducted to compare the PKs and PDs of DigiFab and Digibind when administered 2 h after an intravenous (IV) injection of digoxin. As binding of digoxin by Fab fragments was known to promptly reduce the toxic activity of the drug, the primary endpoint was the free digoxin area under the plasma concentration-time curve (AUC) from 2 h (start of DigiFab/Digibind infusion) to last measurement at 48 h. The secondary endpoints included additional PK parameters for total digoxin and ovine Fab (AUC, systemic clearance, maximum serum concentration [C_{max}], and time to achieve maximum serum concentration [t_{max}]) and serial ECGs for interval analysis (PTQ index). Statistical comparisons were made between mean pharmacokinetic parameters from the DigiFab and Digibind groups using either the Student t-test or a Mann-Whitney rank sum test. Statistical significance was set at a probability value below 0.05 using a 2-tailed test.

It is important to note that DigiFab® was initially called DigiTAb and both these terms have been used interchangeably in the CSRs in the submitted dossier and throughout this evaluation report.

PKs of free serum digoxin: Following administration of DigiFab and Digibind, serum free digoxin levels were reduced from 4.5 ± 3.1 ng/ml and 4.0 ± 0.34 ng/ml (mean value \pm SD), respectively, to levels below the assay limit of quantitation (LOQ) of 0.3 ng/ml for all 16 volunteers. Subsequently, the majority of serum free digoxin concentrations remained below the assay LOQ for several h in both groups (Figure 1). The number of subjects for which the free digoxin concentration remained below the assay LOQ and for which an AUC value could not be calculated was similar between the DigiTAB and Digibind group (2 and 3 subjects, respectively). For some subjects there was a slight rebound in free digoxin concentrations between 8 and 24 h, but the rebound free digoxin concentrations were close to the assay LOQ in most cases (mean peak concentrations of 0.5 ± 0.1 ng/mL for both treatment groups). This is an important consideration, since some subjects had baseline digoxin concentrations slightly above the assay LOQ as well. Overall, only 2.5 ± 1.8 samples per subject were above the free digoxin assay LOQ after DigiTAB administration, which was similar to the 1.9 ± 1.9 samples per subject above assay LOQ in the Digibind group. An additional analysis of AUC for only free digoxin concentrations above assay LOQ was also performed which showed that the mean AUC values between the two groups were not statistically different (10.7 ± 6.1 and 12.7 ± 8.7 for the DigiTAB and Digibind group, respectively). However, there was a large variability reported between subjects, which is likely due to the limited number of free digoxin concentrations above the assay LOQ (Table 2). It was not possible to accurately determine AUC for serum free digoxin between 2 and 48 h, since the majority of samples were below the assay LOQ. Regardless, the AUCs were calculated using an arbitrary value of 0.3 ng/mL for levels below assay LOQ. These AUC values were similar between the two groups (18.3 ± 3.4 and 17.5 ± 3.3 ng/mL *hr for the DigiTAB and Digibind group, respectively), although the data is limited by a sizable inter-individual variance (Table 2).

Figure 1. Serum concentration versus time for free digoxin.

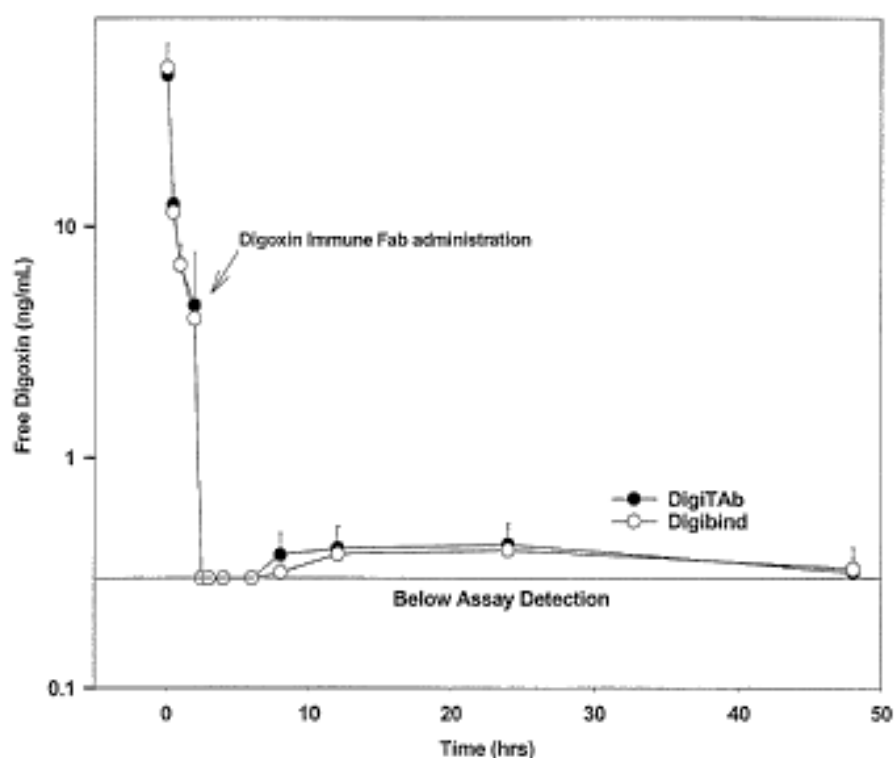


Table 2. Serum free digoxin pharmacokinetic parameters

Subject	No. of Samples above LOQ	AUC ₂₋₂₄ (ng/mL*hr) [†]	AUC ₂₋₂₄ above LOQ (ng/mL*hr) [‡]	Cmax Post-Fab (ng/mL)	Tmax Post-Fab (ng/mL)
DigiTab group					
1	3	18.2	7.9	0.5	8.0
4	0	14.5	NA	NA	NA
6	3	21.4	7.4	0.5	24.0
7	3	16.2	12.9	0.4	24.0
9	2	17.0	5.4	0.4	12.0
12	5	23.9	22.2	0.6	12.0
15	0	14.5	NA	NA	NA
16	4	20.4	8.6	0.5	24.0
Mean	2.5	18.3	10.7	0.5	17.3
SD	1.8	3.4	6.1	0.1	7.4
Digibind group					
2	0	14.7	NA	NA	NA
3	0	14.7	NA	NA	NA
5	2	16.5	4.8	0.4	24.0
8	1	15.7	2.1	0.4	24.0
10	4	23.2	21.1	0.6	12.0
11	4	21.3	18.9	0.5	12.0
13	4	19.4	16.7	0.5	24.0
14	0	14.7	NA	NA	NA
Mean	1.9	17.5	12.7	0.5	19.2
SD	1.9	3.3	8.7	0.1	6.6
p-value	0.3 (NS)	0.6 (NS)	0.6 (NS)	NS	0.6 (NS)

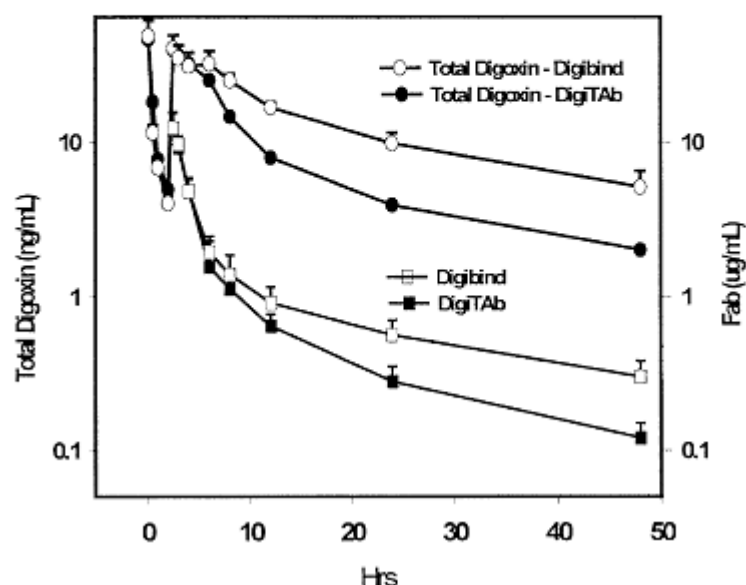
[†] AUC₂₋₂₄ was calculated by assigning concentrations of free digoxin below LOQ as 0.3 ng/mL

[‡] AUC₂₋₂₄ above LOQ, was calculated using post-Fab dosing serum free digoxin concentrations at LOQ only.

PKs of total serum digoxin: Immediately following administration of either Fab product, the total digoxin concentrations rose to similar Cmax values of 44 ± 11 in the DigiTab group and 41 ± 9 ng/mL in the Digibind group. The total digoxin Cmax following digoxin administration was similar to the total digoxin Cmax after DigiTab or Digibind administration, as evidenced by similar pre/post total digoxin Cmax ratios between the two groups (mean \pm SD ratios of 1.0 ± 0.3 in the DigiTab group and 1.2 ± 0.4 in the Digibind group). Following DigiTab or Digibind administration, total digoxin concentrations declined in a slow biexponential fashion. As expected, the concentration-time profile of total digoxin and Fab mirrored one another within each treatment group (Figure 2). This is consistent with what is known about Fab-digoxin pharmacokinetics, since total digoxin concentrations are dependent directly, in a stoichiometric fashion, on Fab serum concentrations.

Figure 2. Serum concentration versus time for total digoxin and Ovine Fab

This graph shows concentrations of total digoxin (ng/mL) and Fab (µg/mL) in serum during the 48-hour sampling period following digoxin dosing (1 mg). At 2 hours, 76 mg of either DigiTab or Digibind was administered over 30 minutes. The assay limit of quantitation is 1.5 ng/mL for total digoxin and 0.055 µg/mL for ovine Fab. Concentrations are shown as mean values with error bars representing standard deviations.



The total digoxin half-life was similar between the DigiTab (18.1 ± 5.3 h) and Digibind groups (21.4 ± 3.8 h), although the limited number of samples and short sampling interval limits the accuracy of the estimated rate constant and subsequently the estimate for half-life. The terminal elimination rate constant for total digoxin was estimated using the last two or three sample times, as determined by visual inspection of the curves.

The AUC values for total digoxin were calculated from the total digoxin concentration-time curve from the 2 h time point and extrapolated to infinity. The estimated AUC values were considered reliable, since only a small percent of the AUC values were extrapolated (range 9 to 28%). Total digoxin AUC values in the DigiTab group (406 ± 102 ng/mL*h) were significantly lower than the values for the Digibind group (769 ± 162 ng/mL*h) ($p < 0.0001$). Area under the first-moment versus time curve (AUMC) values were also estimated. However, as over 50% of the AUMC values were extrapolated based on K_e , the estimate for AUMC and parameters calculated using the AUMC value (Volume of distribution at steady state (V_{dss}) and mean residence time (MRT)) were not reliable and thus not reported.

For both groups, approximately 42% of the total digoxin dose was excreted in the urine between 0 and 24 h after administration. However, about 80% of the recovered digoxin in urine was free digoxin and only 20% was bound to any protein (Fab).

Total digoxin systemic clearance was significantly greater in the DigiTab group at 43.8 ± 3.3 mL/minute compared to 22.5 ± 4.2 mL/minute in the Digibind group ($p = 0.002$).

The observed increase in systemic clearance of total digoxin in the DigiTab group is explained mostly by a similar increase in the renal clearance of total digoxin in this group. The renal clearance of total digoxin was found to be almost 2-fold higher in the DigiTab group (20.8 ± 6.6 mL/min compared to 11.6 ± 2.8 mL/min in the Digibind group; $p = 0.003$).

Comments: Total digoxin systemic clearance was calculated based on the assumption that no digoxin had been eliminated from the body prior to Fab administration. While this is not

technically accurate, the long half-life of digoxin (42 to 43 h) ensures that only a negligible amount of digoxin was lost in the 2 h period between digoxin and Fab administration. Additionally, both groups were treated in the same manner, so for the purpose of comparison, the method is satisfactory.

PKs of DigiTab and Digibind (Ovine Fab): Figure 2 shows serum DigiFab and Digibind concentration versus time profiles. Following intravenous DigiTab and Digibind administration, C_{max} values were similar between the two groups at 12.5 ± 2.8 and 13.0 ± 1.8 ug/mL, respectively (Table 3). Subsequently, DigiTab and Digibind concentrations declined in a slow bi-exponential fashion. Although, the distribution half-life was similar for both products, the DigiTab elimination half-life was shorter at 15.4 ± 3.8 h compared with 23.2 ± 6.1 h for Digibind ($p=0.008$). The terminal elimination rate constant was estimated using only the last two or three sample time points (by visual inspection of the curves); this sparse number of samples and short sampling interval limits the accuracy of the estimated elimination rate constant (K_e) and half-life. The central compartment volume of distribution (V_c) was similar for both products. The AUC values for each Fab product were calculated from the DigiTab or Digibind concentration-time curve from the 2-h time point and extrapolated to infinity. The mean AUC value for the DigiTab group (41.0 ± 8.1 ug/mL*hr) was significantly lower than for the Digibind group (60.5 ± 11.5 ug/mL*hr) ($p=0.002$, Table 3). The estimated AUC values were considered reliable since a relatively small percent of the AUC values were extrapolated (range 4-22%). AUMC values were also estimated, but as over 40% of the AUMC value was extrapolated, the estimate for AUMC and parameters calculated from AUMC (V_{dss} and MRT) were not reliable, and thus not reported. The systemic clearance values for DigiTab (32.0 ± 6.5 mL/minute) were significantly greater than for Digibind (21.6 ± 4.4 mL/minute) ($p=0.002$), which is consistent with the observed lower AUC and higher renal clearance in the DigiTab group. Only a small fraction (2-9%) of either DigiTab or Digibind was found in the urine between the 0 to 24 h sampling period. This is in contrast to the relatively large amount of digoxin (mostly free digoxin) found excreted unchanged in the urine.

Table 3. Serum DigiTab and Digibind pharmacokinetic parameters

Subject	AUC _{0-∞} (µg/mL*hr)	Cl _{total} (mL/min)	t _{1/2α} (hr)	t _{1/2β} (hr)	Vc (L/kg)	Cmax (µg/mL)
DigiTab group						
1	32.0	39.6	1.4	24.1	0.13	7.1
4	31.8	39.9	0.7	13.2	0.06	11.2
6	39.5	32.1	0.7	13.4	0.05	13.3
7	32.8	38.7	0.8	12.4	0.06	10.4
9	51.8	24.5	1.2	15.4	0.07	13.4
12	44.2	28.6	1.1	13.5	0.08	14.6
15	46.5	27.2	1.1	14.7	0.07	14.5
16	49.3	25.7	1.2	16.6	0.08	15.3
Mean	41.0	32.0	1.0	15.4	0.08	12.5
SD	8.1	6.5	0.3	3.8	0.02	2.8
Digibind group						
2	61.3	20.7	1.2	30.2	0.07	11.3
3	53.4	23.7	0.9	33.0	0.06	15.3
5	50.1	25.3	0.8	22.3	0.09	9.6
8	73.7	17.2	1.2	24.4	0.07	13.3
10	42.8	29.6	0.7	15.1	0.06	13.2
11	60.4	21.0	1.1	17.9	0.08	13.0
13	76.1	16.7	1.0	23.6	0.07	14.0
14	66.5	19.0	0.9	19.4	0.07	14.6
Mean	60.5	21.6	1.0	23.2	0.07	13.0
SD	11.5	4.4	0.2	6.1	0.01	1.8
p value	0.002	0.002	0.6	0.008	0.7	0.6

Comments: DigiTab (DigiFab) was shown to bind digoxin in a manner equivalent to Digibind suggesting that DigiFab will be as effective as Digibind at reversing digoxin toxicity. Serum free digoxin levels were reduced to below LOQ in all subjects receiving DigiFab and Digibind. Similar post-Fab administration Cmax values between the groups provide evidence of equivalent binding of digoxin. Differences in Fab and total digoxin pharmacokinetic parameters were demonstrated between the two study groups. Systemic Fab and total digoxin clearance was significantly greater in subjects who received DigiFab compared to those who received Digibind, although the distribution parameters (half-life, volume of distribution) for the Fab products were the same.

The blood sampling strategy was designed to ensure sufficient data was collected to characterize the primary outcome variable, free digoxin. Hence, the determination of some secondary pharmacokinetic variables, like elimination constant for ovine Fab, was compromised due to limited data points, especially at the end of the sampling period.

Much of the difference in systemic clearance of total digoxin appears to be due to its increased renal clearance in subjects receiving DigiFab. Thus, it appears that DigiFab is eliminated from the circulation faster than Digibind, thereby eliminating bound digoxin from the circulation faster as well. Since the most important endpoint for demonstrating that DigiFab and Digibind are equally effective is the binding and neutralization of digoxin, which has been demonstrated, the observed pharmacokinetic differences in total digoxin and Fab are not expected to have a clinical impact.

The primary aim of the study was to demonstrate equivalent bioaffinity of DigiFab and Digibind for their target digoxin, and the most important endpoint for demonstrating that the Fab products are equally effective is the binding and neutralisation of free digoxin in the serum, although the bioaffinity of DigiFab and Digibind for digoxin could not be statistically confirmed as all subjects showed reduction in free digoxin levels to below LOQ. Secondary parameters also

showed similar activity for the two products. Although authorisation of DigiFab is not being sought on the basis of biosimilarity to Digibind, the obvious similarity of the two products means that this comparison is still considered highly relevant to the demonstration of efficacy for DigiFab.

3.3.2.6. *Influence of food*

Not applicable.

3.3.2.7. *Dose proportionality*

Not applicable.

3.3.2.8. *Bioavailability during multiple-dosing*

Not applicable.

3.3.2.9. *Effect of administration timing*

Not evaluated.

3.3.3. Distribution

3.3.3.1. *Volume of distribution*

In Study **TAb007-02**, DigiFab and Digibind showed similar volumes of distribution (0.3 L/kg and 0.4 L/kg for DigiFab® and Digibind®, respectively) indicating considerable penetration from the circulation into the extracellular space. This is consistent with previous reports of ovine Fab distribution, as are the elimination half-life values (15 h and 23 h for DigiFab® and Digibind®, respectively).

3.3.4. Metabolism

Not applicable.

3.3.4.1. *Metabolites identified in humans*

Not applicable.

3.3.5. Excretion

In Study **TAb007-02**, the systemic clearance values for DigiTab (32.0 ± 6.5 mL/minute) were significantly greater than for Digibind (21.6 ± 4.4 mL/minute) ($p=0.002$), which is consistent with the observed lower AUC and higher renal clearance in the DigiTab group. Only a small fraction (2-9%) of either DigiTab or Digibind was found in the urine between the 0 to 24 h sampling period. This is in contrast to the relatively large amount of digoxin (mostly free digoxin) found excreted unchanged in the urine. Thus, it appears that DigiFab is eliminated from the circulation faster than Digibind, thereby eliminating bound digoxin from the circulation faster as well.

3.3.5.1. *Routes and mechanisms of excretion*

Fab-digoxin complexes are cleared by the kidney and reticuloendothelial system.

3.3.5.2. *Mass balance studies*

None.

3.3.5.3. *Renal clearance*

In Study **TAb007-02** in healthy subjects, the renal clearance of total digoxin was found to be almost 2-fold higher in the DigiTab group (20.8 ± 6.6 mL/min compared to 11.6 ± 2.8 mL/min in the Digibind group ($p=0.003$). Much of the difference in systemic clearance of total digoxin appears to be due to its increased renal clearance in subjects receiving DigiFab. Thus, it appears that DigiFab is eliminated from the circulation faster than Digibind, thereby eliminating bound digoxin from the circulation faster as well.

3.3.5.4. Intra- and inter-individual variability of pharmacokinetics

In Study **Tab007-02**, there was a large variability reported between subjects for effects of DigiFab and Digibind on free serum digoxin, which is likely due to the limited number of free digoxin concentrations above the assay LOQ.

3.4. Pharmacokinetics in the target population

Study **Tab007-01** was an open-label, multicentre study to evaluate the pharmacokinetics, pharmacodynamics, and safety of DigiTab in patients with digoxin toxicity. It is an ongoing study and 15 patients have been enrolled and evaluated to date. This study is discussed in detail in the *Pivotal Efficacy* section below.

3.5. Pharmacokinetics in other special populations

3.5.1. Pharmacokinetics in subjects with impaired hepatic function

Not evaluated.

3.5.2. Pharmacokinetics in subjects with impaired renal function

No specific studies have been conducted with the proposed DigiFab in patients with renal impairment. However, pharmacokinetic studies of similar digoxin-specific Fab products (Digibind®, manufactured by GSK and Digidot®, manufactured by Roche) in humans available in the published literature are few in number (Ujhelyi, 1995, Schaumann, 1986). These studies encompass patients with normal renal function, impaired renal function and end stage renal disease. In patients with normal renal function, the volume of distribution of digoxin-specific Fab slightly exceeds extracellular fluid space. Digoxin-specific Fab is eliminated by both renal and non-renal routes in two-thirds to one-third proportion, respectively. In published studies of patients with normal renal function, the terminal elimination half-life ranges from 16-20 h and systemic clearance of 0.324 ml/min/kg (range 0.17 to 0.52 ml/min/kg) (Ujhelyi, 1995).

Pharmacokinetic parameters after digoxin-specific Fab administration in patients with renal dysfunction have been evaluated in a small number of patients (Ujhelyi, 1993). Some controversy exists with regard to precise pharmacokinetic alterations of Fab in this patient population. Renal dysfunction appears to affect the disposition of Fab by decreasing renal clearance by approximately 50% and systemic clearance by up to 75%, while increasing elimination half-life by up to 10-fold. Volume of distribution in patients with renal dysfunction appears unaffected (Ujhelyi, 1993, 1995).

Predictably, end-stage renal disease is also known to hinder the elimination of Fab because large molecules such as Fab are not removed by extracorporeal methods. Systemic clearance in these anephric patients was less than in patients with impaired or normal renal function. While administration of Fab in patients with renal dysfunction and end stage renal disease does not appear to present a safety issue, it does present a clinical challenge regarding how and when to recommence digoxin therapy. There is one case report of recurrence of atrioventricular block due to digoxin in a functionally anephric patient 10 days after its initial reversal by ovine Fab therapy (Wenger, 1991). This clinical event persisted for more than a week. In patients that are functionally anephric, failure to clear the Fab-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated. It is uncertain whether the failure to eliminate the Fab-digoxin complex in severe renal impairment may lead to re-intoxication with digoxin following the release of previously bound digoxin into the blood. However, patients with severe renal failure who receive DigiFab for digitalis toxicity should be monitored for a prolonged period for possible recurrence of toxicity. Monitoring of free (unbound) digoxin concentrations after the administration may be appropriate in order to establish recrudescence toxicity in renal failure patients (Valdez, 1998).

3.5.3. Pharmacokinetics according to age

Specific studies in elderly patients have not been conducted.

3.5.4. Pharmacokinetics related to genetic factors

Not evaluated.

3.5.5. Pharmacokinetics {in other special population / according to other population characteristic}

Not evaluated.

3.6. Pharmacokinetic interactions

Studies of drug interactions have not been conducted with DigiFab.

3.7. Evaluator's overall conclusions on pharmacokinetics

A parallel comparison Study **TAb007-02** evaluated bioequivalence of proposed DigiFab (DigiTAB) to the currently marketed Digibind, in 16 healthy subjects. Both DigiTAB and Digibind are ovine affinity purified Fab antibody fragments raised against digoxin, which have similar *in vitro* binding affinities for digoxin. Since it would be difficult to show bioequivalence in patients, this study was undertaken in volunteers who were given a 1 mg digoxin dose intravenously, observed for two h and then given an equimolar dose of either DigiTAB or Digibind.

Generally, bioequivalence between a currently marketed product and a generic competitor is demonstrated by showing that both have similar distribution and elimination characteristics by serially measuring blood concentrations. However, this may be misleading for antibody products since efficacy depends on binding capacity and affinity. Therefore the aim of Study **TAb007-02** was to demonstrate that DigiTAB and Digibind were equally effective in binding and neutralizing serum free digoxin as this is the best parameter that is indicative of the biological activity and its antidote efficacy. Secondary outcome parameters were pharmacokinetic dispositions of total digoxin and ovine Fab, which were used to support the bioaffinity data.

The primary study endpoint was a reduction in free digoxin serum concentrations to below 0.3 ng/mL, represented by serum free digoxin AUC. Results showed that both Digibind and DigiTAB reduced serum free digoxin concentration to zero in all subjects. The very nature of this endpoint precludes a statistical comparison¹ between groups. These data demonstrate that both Digibind and DigiTAB bind and neutralise digoxin in a similar manner.

The fact that the maximum total digoxin concentrations immediately after the DigiTAB and Digibind infusions were similar to the maximum concentrations immediately after the digoxin infusion is indirect evidence supporting equal bioaffinity for digoxin. Both DigiTAB and Digibind caused most of the administered digoxin to re-distribute back into the central compartment. These data indicate that DigiTAB binds and neutralizes digoxin in a manner equivalent to Digibind and that DigiTAB leads to effective reversal of digoxin toxicity.

It was also observed in this study that systemic Fab and total digoxin clearance were significantly greater in subjects who received DigiTAB compared with those who received Digibind. Much of the difference in systemic clearance of total digoxin appears to be due to an increased renal clearance of total digoxin in subjects receiving DigiTAB. Thus, it appears that DigiTAB is handled by the systemic circulation differently than Digibind; it is eliminated from

¹ This is because free digoxin concentrations below the assay limit of quantitation, if they could be determined, are substantially below clinically meaningful concentrations and the clinical significance of a statistical difference (if it could be measured) would be inconsequential.

the circulation faster than Digibind, thereby eliminating digoxin from the circulation faster as well. However, differences in Fab pharmacokinetic parameters can exist between DigiTab and Digibind independently of similar measures of digoxin neutralisation.

The elimination half-life of DigiFab in renal failure has not been clearly defined, although patients with renal dysfunction have been successfully treated with Digibind. There is no evidence to suggest that the time-course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. Hence, patients with severe renal failure who receive DigiFab for digitalis toxicity should be monitored for a prolonged period for possible recurrence of toxicity and this fact has been adequately addressed in the proposed PI.

Studies of drug interactions have not been conducted with DigiFab.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on digoxin levels and PD effects of digoxin	Study TAB007-02
Secondary Pharmacology		NA
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	NA
	Effect of genetic characteristics	NA
	Effect of age	NA
PD Interactions	Not evaluated	NA
Population PD and PK-PD analyses	Healthy subjects	NA
	Target population	NA

§ Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

DigiFab®, Digoxin-specific antibody fragment f(Ab) (Ovine) powder for injection, is a sterile, purified, lyophilized off-white powder of digoxin-specific antibody ovine Fab (monovalent) immunoglobulin fragments. These fragments are obtained from blood of healthy sheep immunized with a digoxin derivative, digoxin-dicarboxymethoxylamine (DDMA), a digoxin analogue which contains the functionally essential cyclopentaperhydrophenanthrene: lactone ring moiety coupled to keyhole limpet hemocyanin (KLH).

Antibodies produced to DDMA have a greater affinity for digoxin than does digoxin for its sodium pump receptor. When injected into the intoxicated patient, DigiFab binds free digoxin resulting in a shift in the equilibrium away from the tissues, thereby reducing cardiotoxicity. Fab glycoside immune complexes are then cleared by the kidney and reticuloendothelial system.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

DigiFab® has an affinity for digoxin in the range of 10^9 to 10^{10} M⁻¹, which is greater than the affinity of digoxin for its receptor [sodium, potassium adenosine triphosphatase (ATPase)], the presumed receptor for its therapeutic and toxic effects. When administered to the intoxicated patient, DigiFab® binds to molecules of digoxin reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardio-toxic effects.

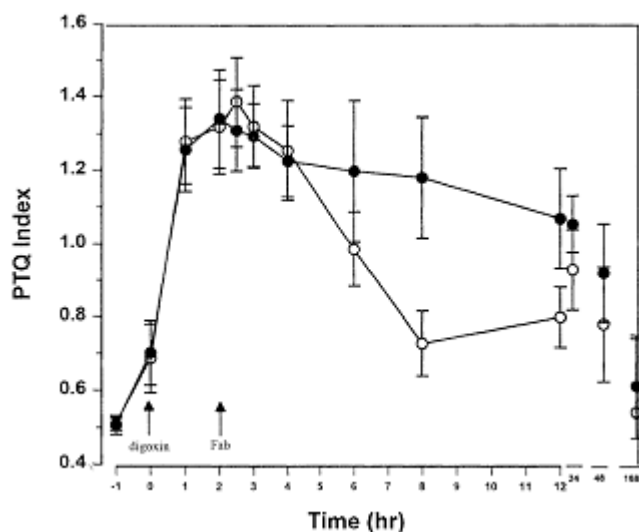
The potency of DigiTAB is standardized *in vitro* by radioimmunoassay saturation analysis. It was estimated that each milligram of digoxin immune Fab would bind approximately 15 ug of digoxin. This was based on comparative *in vitro* and *in vivo* tests of DigiTAB to the currently marketed product Digibind (Glaxo Wellcome).

Comments: Recent revised estimates in the potency of digoxin immune Fab have been made and confirmed. The estimate of potency is currently that 1 mg of Fab will bind approximately 13 ug of digoxin (i.e., approximately 76 mg of Fab will bind 1 mg of digoxin), which is consistent with recent changes in the labelling for Digibind (GSK-Digibind prescribing information).

4.2.2.2. Secondary pharmacodynamic effects

In Study **TAb007-02**, all volunteers showed a decrease in ventricular rate after the digoxin infusion although the extent and duration varied and there was also a large variation in baseline values. After the digoxin infusion, all volunteers showed a decrease in T wave amplitude and most had a shortening of the corrected QT interval (QTc) but there were no consistent changes in the PR interval. Expressing these parameters as a combined function, the PTQ index (PR x Tscore/QTc) increased for all volunteers after digoxin dosing (Figure 3). The PTQ index increased about 250% after digoxin dosing and although this partly decreased after Fab dosing this was not normalized even after seven days. After Fab dosing, the PTQ index decreased in both groups, however, the fall was greater in the Digibind group and the difference from DigiFab was statistically significant at 8 h ($p=0.004$, Wilcoxon rank-sum test, $p > 0.011$, repeated measures analysis with bonferoni correction); this suggested continued effect of digoxin in the DigiTAB group, which is contrary to the actual measurements of free and total digoxin. It took a long time for the PTQ index to return to baseline, as mean values were still elevated after seven days.

Figure 3. PTQ index in the DigiTAB Group (●) and Digibind Group (○). Results are mean values \pm standard error of mean.



This dose of digoxin in healthy volunteers produced no measurable changes in electrolyte levels or vital signs, however there were changes in some ECG measurements. In this study, there were no serious adverse events and many of the events reported were due to paravenous digoxin infusions and general disorders such as influenza like symptoms and tiredness.

Comments: The serum concentrations of total digoxin decreased faster in the DigiFab group and there were no measurable concentrations of free digoxin up to 8 hr, making it difficult to explain the differences observed in PTQ index between the two groups. A diminished response in two of the male volunteers in the DigiTAB group may have been partly responsible for this difference, whereas the two females groups showed a comparable decrease. The diminished response for the male volunteers could not entirely be explained by a greater plasma clearance of Fab or re-occurrence of free digoxin, although, they had relatively low urine Fab concentrations, suggesting greater renal catabolism of the Fab. Published literature on the relationship between PTQ index and digoxin concentration shows that there is considerable inter-patient variability, and that the PTQ index responds slowly to changes in digoxin concentrations (Joubert, 1976).

4.2.3. Time course of pharmacodynamic effects

In Study **TAb007-02**, following both DigiFab and Digibind administration, serum free digoxin levels were reduced from 4.5 ± 3.1 ng/ml and 4.0 ± 0.34 ng/ml (mean value \pm SD), respectively, to levels below the assay limit of quantitation (LOQ) of 0.3 ng/ml for all 16 volunteers. Subsequently, the majority of serum free digoxin concentrations remained below the assay LOQ for up to 8 h in both groups (Figure 1). For some subjects there was a slight rebound in free digoxin concentrations between 8 and 24 h, but the rebound free digoxin concentrations were close to the assay LOQ in most cases (mean peak concentrations of 0.5 ± 0.1 ng/mL for both treatment groups).

4.2.4. Relationship between drug concentration and pharmacodynamic effects

In Study **TAb007-02**, both DigiFab and Digibind were equally effective in binding and neutralising digoxin despite differences in pharmacokinetics of DigiFab and Digibind (ovine Fab). Measurement of serum levels of digoxin have formed the basis of international clinical guidelines that are now the standard for therapeutic drug monitoring routinely performed in patients treated with digoxin. There is a well-established relationship between neutralisation of digoxin and clinical symptom resolution in cases of digoxin toxicity.

4.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not evaluated.

4.2.6. Pharmacodynamic interactions

Not evaluated.

4.3. Evaluator's overall conclusions on pharmacodynamics

DigiFab has an affinity for digoxin in the range of 10^9 to 10^{10} M⁻¹, which is greater than the affinity of digoxin for its receptor [sodium, potassium adenosine triphosphatase (ATPase)], the presumed receptor for its therapeutic and toxic effects. When administered to patients with digoxin toxicity, DigiFab binds to molecules of digoxin reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardio-toxic effects. Fab-digoxin complexes are then cleared by the kidney and reticuloendothelial system.

Both DigiFab and Digibind were equally effective in binding and neutralising digoxin despite differences in pharmacokinetics of DigiFab and Digibind (ovine Fab). DigiFab reduced free digoxin levels to below LOQ for up to 8 h after which there was some rebound of free serum digoxin levels (but these were still close to the LOQ).

In Study **TAb007-02** after the digoxin infusion there were no consistent changes in the PR interval, but the corrected QT (QTc) interval shortened and all patients had T-wave depression. Combining these parameters, the PTQ index increased about 250% after administering digoxin and had not returned to baseline values even after seven days. After Fab administration, the PTQ index decreased in both the Digibind and DigiTA b groups, although there was a statistically significant difference at eight h after digoxin dosing between the Digibind and DigiTA b group, with a lower PTQ in the Digibind group. This was partly due to a diminished response in two of the male volunteers in the DigiTA b group, whereas the two females groups showed a comparable decrease. The diminished response for the male volunteers could not entirely be explained by a greater plasma clearance of Fab or re-occurrence of free digoxin, however, they had relatively low urine Fab concentrations, suggesting greater renal catabolism of the Fab.

5. Dosage selection for the pivotal studies

Not applicable.

6. Clinical efficacy

6.1. Indication 1

Treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias not responsive to atropine and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

6.2. Pivotal efficacy studies

Of the 3 studies included in the dossier submitted by the sponsor, only 2 studies (PR007-CLN-rpt003 and TAb007-01) involved patients (Study **TAb007-02** was conducted in healthy subjects). There were no randomised, controlled studies due to the nature of the proposed indication and both the studies in patients only involved historical control (TA b007-01) or a

retrospective review of clinical cases (PR007-CLN-rpt003). Hence, these studies may not meet the criteria of being 'pivotal' studies under regulatory guidelines, but they are pivotal to the evaluation of this submission and have been discussed in this section of the evaluation report due to the following reasons:- (1) the rare and emergency nature of the proposed indication of digoxin toxicity, (2) these two clinical studies (and Study **TAb007-02** in healthy subjects) are the only studies specifically conducted with DigiFab® worldwide, and (3) the sponsor does not intend to conduct further clinical studies of DigiFab.

6.2.1. Study TAb007-01

6.2.1.1. Study design, objectives, locations and dates

This study was a historically controlled, open-label, multicentre trial of DigiTAB administered to patients of any age with potentially life-threatening cardiac toxicity caused by an acute or chronic ingestion of digoxin. Upon recommendation by, and in agreement with representatives of the FDA, Protherics has completed database entry of a total of 15 patients enrolled in this study².

The trial objectives were to evaluate the pharmacokinetics, pharmacodynamics and safety of DigiTAB as compared to historical control data available for Digibind, the marketed comparable agent which is also a Digoxin Immune Fab (Ovine) manufactured by Glaxo Wellcome.

The primary objective was to document the reduction of serum free digoxin to less than 0.5ng/mL by the end of the DigiTAB infusion (time "0" h).

Secondary objectives included: Evaluation of clinical therapeutic response, that is, pharmacodynamic response, as measured by the percent of patients showing resolution in digoxin-induced arrhythmias, high-grade conduction block, and/or severe neurological signs and symptoms at 2 and 4 h after DigiTAB treatment; Characterisation of the pharmacokinetic disposition of digoxin and DigiTAB in patients with life-threatening toxicity as measured by total and free serum digoxin, total and free serum Fab, and urinary digoxin and Fab concentrations; and Characterization of other pharmacologic activity, such as clinical response profile as reflected by serum creatinine. A tertiary objective was assessment of the safety of DigiTAB.

6.2.1.2. Inclusion and exclusion criteria

Patients demonstrating acute or chronic digoxin toxicity in the following manner: ECG changes consistent with hyperkalemia in the face of digoxin toxicity; hemodynamic compromise associated with arrhythmias or requiring the use of epinephrine, atropine or antiarrhythmic agents; serum digoxin concentration > 4.5 ng/mL with symptoms of digoxin toxicity; digoxin-induced bradycardia unresponsive to atropine or signs and symptoms of profound neurological abnormalities; or a known ingestion in a child of > 0.1 mg/kg of digoxin.

The main exclusion criteria were: Current or prior treatment with Digibind, or prior treatment with DigiTAB; Current or planned use of any experimental medication, or use of any experimental medication within four weeks prior to entering this study; Inability to give informed consent as defined by criteria established by the Institutional Review Board (IRB) of the Investigator's institution; Known history of hypersensitivity to sheep-derived products, except for minimal irritation reactions to sheep wool; previous enrolment in this study.

6.2.1.3. Study treatments

The dose of DigiTAB was calculated to determine the amount needed to perform approximately equimolar neutralization of the total body burden (TBB) of digoxin, based on either the serum concentration or known amount of digoxin ingested. If the amount ingested was unknown and

² Although this study is ongoing, any additional patients enrolled subsequent to 3 February 2000 will not be included in the final database as discussed and agreed upon with representatives of the FDA. If any additional patients are enrolled in this study, adverse event and other safety outcomes will be reported to the FDA separate from this report.

digoxin concentration was not available, the initial dose in adults was 20 vials. Patients were administered a single dose of DigiTAB (with repeat doses allowed at the investigator's discretion) and followed for up to 30 days post-dosing for safety, pharmacokinetics and clinical response. No control treatment was administered during the study. However, historical data from Digibind studies was used as a control.

6.2.1.4. Efficacy variables and outcomes

Efficacy was measured using pharmacokinetic and clinical parameters. Pharmacokinetic evaluations included analysis of free and total serum and urine digoxin concentrations as well as serum and urine Fab concentrations. Clinical response to DigiTAB was evaluated using the ECG and rhythm strip interpretations, measurement of serum electrolytes, and clinical evaluations.

The primary efficacy outcome was the reduction of serum free digoxin concentrations to <0.5 ng/mL, a concentration that was determined to be below the clinically therapeutic range. Serum samples for determination of free digoxin were drawn by the Investigator's staff immediately prior to DigiTAB administration and upon completion of DigiTAB infusion at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 48, 72 and 96 h after the end of the DigiTAB infusion.

The secondary objective was clinical therapeutic response, as measured by the percent of patients with resolution of digoxin-induced toxicity at two and four h following DigiTAB administration. Response to study drug infusion was evaluated by the Investigator and recorded at the end of the DigiTAB infusion (time "0"), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 h after the end of the DigiTAB infusion. Assessments of response³ at each time-point included ECG and rhythm strip, vital signs and electrolytes.

An additional secondary objective of this study was to characterize the pharmacokinetic disposition of DigiTAB (Fab) and of free and total digoxin in patients with digoxin toxicity receiving DigiTAB. Blood samples were drawn immediately before infusion of the study drug, upon completion of the DigiTAB infusion (time "0" h), and at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, 72, and 96 h after the end of the DigiTAB infusion. Urine was collected as a spot sample at baseline, and pooled collections at 0-12, 12-24, 24-48, 48-96 h following DigiTAB infusion.

6.2.1.5. Randomisation, blinding methods

This was an open-label non-concurrently controlled trial and all eligible patients received active treatment.

6.2.1.6. Sample size, statistical methods

The planned sample size for this study was 25 patients, based on practical limitations of patient accrual. Regulatory authorities have acknowledged that fewer than the planned 25 patients may be adequate for completion of the study, given the difficulty in enrolling the type of patients required.

Patients with a serum free digoxin concentration less than 0.5 ng/mL by time "0" h (at the end of DigiTAB infusion) were considered a treatment success. The percent of patients achieving this primary endpoint was described and qualitatively compared to historical data available from the literature for Digibind. A non-compartmental pharmacokinetic model was used to calculate PK variables. The percent of patients achieving a complete clinical response ("resolved") by 4 h following DigiTAB dosing has been described. As historical data was only

³ The following definitions were used to evaluate the time course of overall clinical response for each patient: Resolved: Complete resolution within 4 h of all signs and symptoms of digoxin toxicity present before DigiTAB treatment. Life threatening neurological signs and symptoms, and cardiac dysrhythmia must have resolved within an accelerated time course (within minutes to h after treatment) compared to the patient's baseline condition (e.g., normal electrocardiogram for that patient). Not Resolved: Symptoms or signs of digoxin toxicity were still present.

available in summary form from published literature sources, only a qualitative comparison was done to historical data with Digibind.

6.2.1.7. Participant flow, protocol violations/deviations

This final study report includes data from a total of 15 patients enrolled in the study between January 1998 and June 1999. All 15 patients treated with DigiTAb remained hospitalized for at least 24 h and were eligible for safety and efficacy analyses. Five patients did not complete the 26 to 30 day follow-up evaluations and were lost to follow-up.

There were no major protocol deviations. There were some minor deviations mainly related to timing of blood sampling, missing data, and visits outside the protocol-specified window. None of these minor protocol deviations affected the overall objectives or the integrity of the study.

6.2.1.8. Baseline data

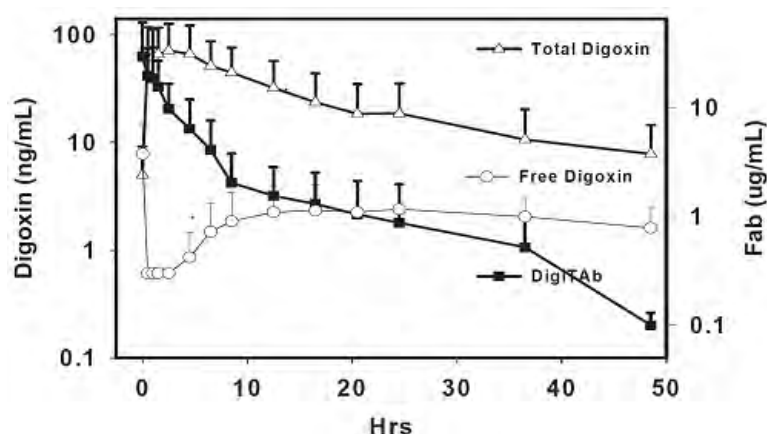
DigiTAb patients were primarily elderly Caucasian adults with digoxin toxicity mostly derived from chronic therapeutic dosing. Six (40%) patients were male and 9 (60%) were female and the mean age was 64 years (range 40 to 85 years) (Table 5). Digoxin ingestion was reported as chronic for 10 (67%) patients, suicidal for 5 (33%), acute on chronic for 3 (20%), acute for 1 (7%), and accidental for 1 (7%). Males accounted for 3 of the 5 (60%) suicidal ingestion cases, while females accounted for 7 of the 10 (70%) chronic ingestion cases. Nine patients had hemodynamic compromise as their digoxin intoxication manifestation upon enrolment. Seven patients had a digoxin level >4.5 ng/mL, two of which also had hemodynamic compromise. All other digoxin toxicity manifestations occurred in conjunction with either of those two criteria plus one of the following: cardiovascular compromise, bradycardia, and neurologic abnormalities. Four patients had ECG changes consistent with hyperkalemia. Thirteen of the DigiTAb patients were under treatment with digoxin for underlying heart dysfunction: 5 for atrial fibrillation, 3 for congestive heart failure, 2 for a combination of both and 1 for fast heart rhythm, 1 for a combination of fast heart rhythm and coronary artery disease, and 1 for an unclear reason.

Table 5. Study TAb007-01 Demographics

Demographic Parameter		(n = 15)
Age (years)	Mean	64 ± 15
	Median	67
	Range	40 – 85
Gender	Male	6 (40%)
	Female	9 (60%)
Weight (kg)	Mean	71.6 ± 20.4
	Male (mean, range)	82.7 (60.0 – 119.2)
	Female (mean, range)	64.2 (53.0 – 76.2)
Height (cm)	Mean	165 ± 9
	Male (mean)	172
	Female (mean)	160
Race	Caucasian	15 (100%)

6.2.1.9. Results for the primary efficacy outcome

Of the 13 patients in this study who had sufficient serum collected at the end of DigiFab infusion (0 h), free serum digoxin concentrations decreased to a level at or less than the assay limit of quantitation (0.3 ng/mL) in all 13 patients. Two patients did not have a serum digoxin sample collected until 0.5 h after Fab infusion; both of these patients' serum free digoxin concentration at this time was less than 0.3 ng/mL. All patients receiving DigiTAb maintained free serum digoxin concentrations at or less than 0.3 ng/mL for an average of 9.6 h after Fab infusion (range: 4.5 to 24.5 h). The maximum rebound free digoxin concentration averaged 1.4 ± 0.8 ng/mL and ranged from 0.3 to 2.8 ng/mL. The time to maximum free serum digoxin rebound averaged 15.1 h (range 6.5 to 36.5 h) (Figure 4).

Figure 4. Serum concentration of digoxin (free and total) and Fab over time

6.2.1.10. Results for other efficacy outcomes

6.2.1.10.1. Secondary efficacy parameter: clinical therapeutic response

A secondary study objective was to evaluate the clinical therapeutic response to DigiTab administration as measured by the percent of patients with clinical response of digoxin-induced arrhythmias, high-grade conduction block, and/or severe neurological signs and symptoms at two and four h post-DigiTab. Investigators classified 6 of 15 patients (40%) as having complete resolution of digoxin toxicity within 2 h of DigiTab administration, with one additional patient resolving by 3 h. Digoxin toxicity resolution was maintained in these 7 patients (47%) at 4 h. Fourteen patients (93%) were classified by investigators as having resolved their digoxin toxicity by 20 h. One patient was judged a non-responder after 24 h; this patient had continuing ECG abnormalities at the 30 day follow-up visit.

The method used to classify the ECG recordings did not discriminate between degrees of abnormality and therefore was not interpretable in terms of efficacy. To address this concern, an independent blinded panel of three physicians (one board-certified cardiologist and two board-certified emergency medicine physicians)⁴ reviewed all patient ECG and rhythm strip recordings (without knowledge of clinical or study details) to determine how these two factors responded over time, irrespective of other clinical factors. The review panel determined that 10 of 15 patients (67%) had ECG abnormalities that improved during the 24 h study period. All 10 improved within 4 h after the DigiTab infusion. Six of these patients maintained improved ECG recordings throughout 24 h of hospitalization. The other four patients had ECG abnormalities that worsened within 24 h of their initial improvement. It is uncertain if worsening was attributable to recurrence of digoxin toxicity or to loss of digoxin therapeutic effect on underlying cardiac dysfunction. The review panel determined that the remaining 5 patients had ECG abnormalities that were unchanged from baseline throughout hospitalisation.

Serum potassium data were also evaluated to characterize the clinical response. While mean potassium values appear slightly higher at baseline and at 0 and 0.5 h when compared to the later time-points, formal statistical tests were not applied due to the small number of subjects.

In addition, most patients enrolled had chronic rather than acute toxicity and would not be expected to have hyperkalemia. Among the 4 patients presenting with serum potassium concentrations outside or at upper limits of the normal range, serum potassium began to decrease within 30 minutes of DigiTab administration.

⁴ The physicians were blinded to the DigiTab study and did not know that patients had digoxin toxicity. Physicians were asked to determine whether the ECG recording for each time point was abnormal and to determine how it compared to the recording for the previous time point using the following scale: Improved = ECG abnormalities have improved from the previous time point; Worsened = ECG abnormalities have worsened from the previous time point; Unchanged = ECG abnormalities have not changed from the previous time point.

A secondary objective of this study was to characterise the pharmacokinetic disposition of total digoxin and Fab in patients receiving DigiTab. All patients, as expected, had total serum digoxin increase 10 to 21-fold from baseline (range = 9.6 to 20.5, median = 13.9) (Figure 4). The elimination half-life of total digoxin averaged 22.8 ± 10.2 h in patients who received DigiTab, although in several cases only 2 data points were used to estimate this parameter, making the estimates less reliable. Other pharmacokinetics parameters, such as volume of distribution and clearance were not calculated because the extrapolated portions of AUC and AUMC were greater than 20% in many cases, making the data somewhat unreliable for calculating these parameters.

The individual serum Fab concentration-time curves do not consistently follow a log-linear decay (Figure 4); the curves contain a variety of peaks, dips, and plateaus. There was a wide range of DigiTab doses administered. DigiTab clearance averaged 33.9 ± 23.1 mL/min (0.4 ± 0.2 mL/min/kg) and half-life averaged 16.9 ± 6.6 h. Cmax values ranged from 8.2 to 118 ug/mL, reflecting the large range of doses administered. Tmax ranged from 0.5 to 4.5 h. These values are similar to data available for the healthy volunteer study of DigiTab (Protocol **TA007-02**), where clearance and half-life were 32.0 ± 6.5 mL/min and 15.4 ± 3.8 h, respectively, although the variance is much greater for the patients. Due to limitations of the digoxin and Fab serum and urine data, pharmacokinetic interpretation of the urine data would not be meaningful and was not performed.

Comments: Overall, in spite of the limitations of the pharmacokinetic data, serum free digoxin concentrations, the primary efficacy endpoint for this study, fell to or below the level of detection (0.3 ng/mL) following DigiTab administration in all patients. Seven of 15 (47%) patients treated had complete resolution of digoxin toxicity by 4 h after DigiTab administration and 14 (93%) patients had complete resolution by 20 h. Ten patients (67%) showed improvement in their ECG within 4 h of DigiTab administration.

6.2.2. Study PR007-CLN-rpt003

6.2.2.1. Study design, objectives, locations and dates

PR007-CLN-rpt003 was a descriptive study for a single group of patients that were treated with one or more doses (as required) of DigiFab in accordance with standard of care between January 1, 2003 and July 31, 2006.

The main objectives of this retrospective study was to assess the effectiveness of DigiFab in treating human patients with life-threatening digoxin toxicity at 0 to 4 h, >4 to 12 h, >12 to 24 h and >24 to 72 h after completion of therapy. The secondary objective was to evaluate the safety of DigiFab by characterizing specific drug-related AEs occurring during or after treatment.

Demographics, treatment, and outcome data were collected from medical records of patients treated with DigiFab for life-threatening digoxin toxicity. Response to treatment (such as efficacy) was evaluated as the rates of improvement in cardiac (judged by review of ECG and rhythm recordings by an expert consensus panel), gastrointestinal, and neurological manifestations by 72 h after the end of treatment. Rates of improvement in general clinical status as well as normalization of serum potassium levels were also assessed. Safety was determined by the frequencies and rates of serious and non-serious drug-related AEs.

As this was a retrospective study, only basic descriptive statistics (such as rates and measures of central tendency) were calculated. No analytical or comparative statistical tests were performed. This retrospective study was designed and conducted following clinical development discussions with the UK Medicines and Healthcare Products Regulator Agency (MHRA) (the second country in which marketing authorisation was sought). The study was conducted in the USA because, at the time, this was the only location where DigiFab was marketed and where there would be any reasonable probability of obtaining data on a sufficient number of patients.

Comments: There was significant difficulty recruiting patients into this retrospective study because often the brand name DigiFab was not used to identify which Fab product was administered, so the enrolment was limited to those patients for whom it could be confirmed that DigiFab was definitely administered. It was not practically feasible to undertake a survey of all centres where DigiFab was potentially administered; therefore, the sites utilised were limited to the centres that had a known investigator within the toxicology investigator network. In addition, the investigators had to be trained to extract data which limited the number of sites for resource reasons. Finally, the inclusion and exclusion criteria limited patient participation in the study based on whether these data were available in the medical charts.

6.2.2.2. *Inclusion and exclusion criteria*

The main inclusion criteria were: Patients of any age or gender, treated with DigiFab between January 1, 2003 and July 31, 2006; Serum digoxin level ≥ 2 ng/mL before the start of DigiFab therapy; Patient treated for one or more of the following life-threatening cardiac abnormalities, evident on ECG or rhythm strip (when available), within six h before the start of DigiFab: (1). Ventricular rate < 45 bpm, (2). 2nd degree heart block, (3). 3rd degree/complete heart block, (4). Asystole (ECG/rhythm strip may not be available), (5). Ventricular tachycardia (ECG/rhythm strip may not be available), (6). Ventricular fibrillation (ECG/rhythm strip may not be available).

The main exclusion criteria were: Patient treated for intoxication of digitalis-containing compound other than digoxin (such as, purple foxglove, digitoxin); Patients with a pacemaker prior to the start of DigiFab (during baseline ECG).

6.2.2.3. *Study treatments*

The usual dose for adults and children over 20 kg may vary between one half of a vial (20 mg DigiFab) to 20 vials (800 mg DigiFab). More vials may be needed dependent upon the amount of digoxin consumed. The average dose used during clinical testing was 5 vials. A range of 1 to 10 vials (40 mg per vial) was used in the retrospective study PR007-CLN-rpt003.

6.2.2.4. *Efficacy variables and outcomes*

Clinical efficacy was evaluated by responses (pre/post therapy) of five clinical parameters during four post-treatment time intervals (0 to 4 h, >4 to 12 h, >12 to 24 h, and >24 to 72 h), relative to baseline. The five parameters included gastrointestinal signs and symptoms, neurological signs and symptoms, general clinical effects, cardiovascular signs, and serum potassium levels. Responses were expressed as the total proportion of patients with available data.

Rates for safety and efficacy endpoints were calculated and summarised. No analytical or comparative statistical procedures were performed.

Comments: One of the limitations of this retrospective review study was that measurement of serum digoxin levels post-treatment was not routinely performed.

6.2.2.5. *Randomisation and blinding methods*

As the study was retrospective, there were no patient dropouts. There was no blinding of patients or investigators to treatment. All pre-baseline and post-treatment ECG and rhythm recordings were randomised to allow for blinded review by an expert panel.

6.2.2.6. *Analysis populations, sample size and statistical methods*

The required sample size for this study was based on discussion with the United Kingdom (UK) MHRA; no statistical power calculations were performed. The desired sample size was 10 to 20 patient medical records. Only 14 (28%) records from two of the hospitals met all entrance criteria and were abstracted onto CRFs. Only records from two of the named sites met the inclusion criteria. An expert panel of board-certified physicians reviewed the records and

consensus was reached regarding the presence of one or more life-threatening cardiac manifestations from digoxin toxicity on baseline electrocardiograms or rhythm strip recordings.

6.2.2.7. Participant flow, major protocol violations/deviations

A total of 50 patient medical records were screened for inclusion and exclusion criteria between 1 January 2003 and 31 July 2006. Only 14 (28%) records met all entrance criteria and were analysed. There were no patient drop-outs as the study was retrospective.

There were no protocol deviations associated with the conduct of this study.

6.2.2.8. Baseline data

The majority of patients included in this study were elderly Caucasian adults. There was an equal distribution of patients by gender. All 14 patients were taking digoxin for a prescribed indication prior to treatment and all were treated for toxicity related to accidental/unintentional, chronic (ingestion of a therapeutic dose accumulating over a period greater than 24 h) exposure. As specified in the inclusion criteria for this study, all patients had one or more life-threatening cardiac rhythm abnormalities and a serum digoxin level of at least 2 ng/mL. Slow ventricular rate (<45 beats per minute (bpm)) was present in twelve (86%) patients, one (7%) patient had complete (third degree) heart block, and asystole was present in one (7%) patient.

All patients received at least one intravenous dose of DigiFab: 13 patients received a single dose and one patient [information redacted] received a second dose 28.5 h after the end of the first dose. The number of vials of DigiFab ranged from 1 to 7 per dose (median = 2 vials). The duration of infusion was documented in only five (36%) of the medical records included in this study; all known durations were 30 minutes. Eleven (79%) patients received one or more concomitant therapies before, during, and/or after DigiFab.

6.2.2.9. Results

At the first post-treatment interval (0 to 4 h), three of seven (43%) patients evaluable for cardiac response showed improvement. Four of six (67%) evaluable patients demonstrated improvement during the >4 to 12 h interval and seven of nine (78%) evaluable patients during the >12 to 24 h interval. There was no worsening of cardiac abnormalities at any post-treatment time interval in any patient. The rate of improvement by 72 h after the end of treatment was 100% (11/11). All 11 evaluable patients within the >24 to 72 h time interval showed resolution of cardiac rhythm abnormalities that were present at baseline (Table 6). Three patients did not have sufficient data with which to determine efficacy by 72 h post-treatment. One patient [information redacted] did not show correction of slow ventricular rate (<45 bpm) during the first two post-treatment time intervals and had no data to assess improvement during the last two time intervals. This patient had advanced metastatic lung cancer and within 24 h after admission, was treated with "comfort measures only", per hospice care. Therefore, little medical information was available in the medical record with which to judge outcome after DigiFab therapy. Two patients⁵ did not have cardiac response data available at any post-treatment time interval.

⁵ One patient could not be assessed due to pacing of cardiac rhythm after treatment. But, this patient did show improvement in all secondary efficacy endpoints by >12 to 24 h post-treatment. Another patient was discharged and returned to the nursing home less than two h after DigiFab therapy

Table 6. Cardiac response to DigiFab therapy. All responses are relative to baseline. [Patient ID column has been redacted from this table.]

Baseline	0 to 4 hrs	>4 to 12 hrs	>12 to 24 hrs	>24 to 72 hrs
VR	U	I	I	I
VR	U	ND	U	I
VR	I	I	I	I
VR	I	I	I	I
VR	ND	U	U	I
VR	ND	ND	ND	I
HB3	ND	ND	I	I
VR	ND	ND	ND	ND
VR	U	I	I	I
VR	ND	ND	I	I
VR	ND	ND	ND	ND
VR	I	ND	I	I
A	ND	ND	ND	I
VR	U	U	ND	ND
-	3/7 (43)	4/6 (67)	7/9 (78)	11/11 (100)

Cardiac abnormalities: VR=ventricular rate; A=asystole; HB3=3/complete heart block; I=improved; U=unchanged; W=worsened; ND=no data available; * Patient received a second dose of DigiFab 28.5 hrs after the end of the first dose; T=patients with no data (ND) were not included in the rate of improvement calculation for each interval.

Comments: Though it appears that only 3/7 (43%) patients demonstrated cardiac improvement by 4 h after treatment, it is noted that four patients had no chance of demonstrating improvement in cardiac abnormalities within 4 h after therapy because there were no post-treatment ECG or rhythm strips available until the >12 to 24 h or >24 to 72 h.

Six (43%) patients were excluded from assessment of gastrointestinal response as there were no gastrointestinal manifestations of digoxin toxicity (abdominal pain, anorexia, diarrhoea, nausea, vomiting, and/or other signs or symptoms identified by the investigator) at baseline. Improvement was observed in two of seven (29%) evaluable patients during the first post-treatment interval (0 to 4 h), two of six (33%) evaluable patients during the >4 to 12 h interval and four of six (67%) evaluable patients during the >12 to 24 h interval. The rate of improvement by 72 h after the end of treatment, relative to baseline, was 100% (6/6). All 6 evaluable patients within the >24 to 72 h time interval showed improvement in gastrointestinal effects of digoxin toxicity relative to baseline (Table 7). Two patients with abnormalities present at baseline did not have sufficient data with which to determine efficacy by 72 h after treatment.

Table 7. Gastrointestinal response to DigiFab therapy. All response are relative to baseline. [Patient ID column has been redacted from this table.]

Abnormalities at Baseline (Y/N)?	0 to 4 hrs	>4 to 12 hrs	>12 to 24 hrs	>24 to 72 hrs
Y	U	U	I	I
N	U	U	U	U
Y	I	I	I	I
N	U	U	U	U
Y	U	U	U	I
N	U	U	U	U
Y	U	U	U	I
Y	U	U	I	I
N	U	U	U	U
Y	I	I	I	I
Y	U	ND	ND	ND
N	ND	ND	ND	ND
N	U	U	U	U
Y	ND	ND	ND	ND
-	2/7 (29)	2/6 (33)	4/6 (67)	6/6 (100)

I=improved; U=unchanged; W=worsened; ND=no data available; ** Patient was sedated and intubated at baseline, therefore exact gastrointestinal abnormalities could not be identified; however improvement relative to baseline was noted in the medical record at each post-treatment interval (therefore, it was assumed that the patient was in an abnormal state at baseline; * Patient received a second dose of DigiFab 28.5 hrs after the end of the first dose; T=patients with no data (ND) were not included in the rate of improvement calculation for each interval.

Overall, 6 patients⁶ were excluded from the analysis of neurological response. One of nine (11%) evaluable patients showed improvement at the first post-treatment interval (0 to 4 h), three of eight (38%) evaluable patients during the >4 to 12 h interval and six of eight (75%) evaluable patients during the >12 to 24 h interval. The rate of improvement by 72 h after the end of treatment was 88% (7/8).

All patients were eligible for assessment of the endpoint of rate of improvement in general clinical disposition by 72 h after the end of treatment as general clinical status at baseline was considered abnormal for all patients at baseline. Improvement was observed in three of ten (30%) evaluable patients during the first post-treatment interval (0 to 4 h), five of nine (56%) evaluable patients during the >4 to 12 h interval and eight of ten (80%) evaluable patients during the >12 to 24 h interval. The rate of improvement by 72 h after the end of treatment, relative to baseline, was 100% (9/9). Four patients with abnormalities at baseline were not included in this rate calculation because no data were available with which to judge improvement within the >24 to 72 h time interval.

The final secondary efficacy endpoint for this study was the rate of normalisation of serum potassium levels by 72 h after treatment. Six of 14 patients did not have abnormal potassium levels at baseline and were excluded from the efficacy analysis. Baseline levels for the remaining 8 patients were above the upper limits of normal (for example, >5.0 mmol/L, hyperkalemia). One of four (25%) patients with evaluable data had potassium levels that returned to normal relative to baseline at the 0 to 4 h post-treatment interval. Two of five (40%) evaluable patients

⁶ One patient did not have any neurological manifestations of digoxin toxicity (anxiety, dizziness, fatigue, malaise, headache, and visual disturbances, and/or other signs or symptoms identified by the investigator) at baseline and were excluded from assessment of neurological response. Two patients were sedated and intubated at baseline; these patients were also excluded because presence of abnormalities could not be determined. Three patients with abnormalities at baseline were not included in this calculation due to absence of data during all post-treatment intervals.

had normalised potassium levels during the >4 to 12 h interval and five of six (83%) evaluable patients during the >12 to 24 h interval. The rate of normalisation in potassium levels by 72 h post-treatment was 86% (6/7). One patient with hyperkalemia at baseline was not included in this calculation due to absence of data during the >24 to 72 h interval.

Serum digoxin levels were measured prior to therapy in all subjects included in this study (per study inclusion criteria), but no baseline serum free digoxin levels were measured in any patient. Post-treatment free digoxin levels were documented in only two patients, and at only one time point for each. Both patients showed only trace levels of free digoxin.

Comments: The results from this retrospective study of 14 patients corroborate efficacy and safety findings from the prospective DigiFab study of 15 patients (see above). For all efficacy endpoints, there was a progressively increasing rate of improvement over time across all patients with evaluable data. By the end of the 72-h post-treatment time interval, 100% (11/11) of evaluable patients demonstrated cardiac improvement, 100% (6/6) demonstrated improvement in gastrointestinal abnormalities, 88% (7/8) showed improvement in neurological abnormalities, general clinical disposition improved in 100% (9/9) of evaluable, and the rate of normalisation of serum potassium levels was 86% (6/7). No patients demonstrated worsening of any efficacy endpoint during any time interval for which data were available after treatment.

A clinical trial of 150 patients with life-threatening digoxin toxicity (Antman et al, 1990) found that most patients that responded to treatment with Digibind (similar product to DigiFab) showed a complete clinical response by 4 h after the end of the infusion. Half of the patients in that trial (49%) were treated for large single overdose of digoxin or digitoxin; those patients may be more likely to show a more rapid response to Fab therapy than patients receiving long-term digoxin therapy. In contrast, all patients in the present study and 10/15 (67%) patients from the DigiFab prospective study had digoxin toxicity derived from chronic therapeutic dosing. Nonetheless, all 10 patients from the DigiFab prospective study with resolution of ECG abnormalities also showed improvement by 4.0 h after the end of therapy, whereas only 3 of 7 (43%) patients in this retrospective study appeared to demonstrate cardiac improvement (based on consensus panel judgments of available ECG and rhythm strips) by 4 h after therapy. The apparent delay in response by some patients in this study may be a reflection of available data with which to judge response during the 0 to 4 post-treatment time interval. Differences in underlying health conditions and/or type and severity of toxic effects⁷ may also be contributing factors to differences in results between studies. It is not possible to rule out that resolution of toxic effects was related to time (such as metabolism and elimination of digoxin via biological processes), but this is a limitation inherent to uncontrolled, retrospective studies.

6.3. Other studies

Not applicable.

6.4. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

6.5. Evaluator's conclusions on clinical efficacy

The three studies submitted in this dossier (TAb007-01, TAb007-02 and PR007-CLN-rpt003) were adequate considering the rare and emergency nature of the proposed indication of digoxin

⁷ (DigiFab prospective study: 4 patients (26%) had neurological abnormalities, 5 (33%) were bradycardic, and 9 (60%) had abnormal renal function; Current study: 11/12 (92%) evaluable patients had neurological abnormalities, 12/14 (86%) were bradycardic, and 11/13 (85%) had abnormal renal function.

toxicity. It is acknowledged that these three clinical studies are the only ones to have been specifically performed on DigiFab® worldwide. Life-threatening digoxin toxicity is a rare condition and DigiFab has been designated an orphan medicinal product in Australia. A total of 37 subjects or patients received DigiFab in the clinical program.

The most important clinical endpoint in examining the efficacy of DigiFab is the assessment of serum free digoxin concentrations. Standard pharmacologic texts such as Goodman and Gilman describe the therapeutic effects of digoxin as being related to its serum concentrations. There is a well-established relationship between neutralisation of digoxin and clinical symptom resolution. Therefore, digoxin neutralisation determined by assessment of serum digoxin levels is an appropriate primary endpoint for assessment of Fab efficacy in the prospective Study TAb007-01.

The efficacy of DigiFab in terms of clinical resolution of symptoms associated with digoxin toxicity was also evaluated in these studies. The ability to determine whether clinical symptoms have resolved will depend on whether the symptoms are due only to digoxin toxicity or are confounded by an underlying renal or cardiac condition. Such underlying conditions are more likely to be present in patients with chronic digoxin toxicity who have been taking digoxin to treat underlying disease than in those with acute toxicity following an attempted suicide or an overdose. The resolution of clinical symptoms will be more clearly and rapidly seen in patients who have acute toxicity and no underlying condition than in those who have chronic toxicity.

The study designs had certain limitations and it is acknowledged that comparison with historical data presents some difficulties, as does a retrospective review, and patient numbers were limited due to the nature of the condition.

In Study **TAb007-01** involving 15 patients with digoxin toxicity, serum free digoxin concentrations (the primary efficacy endpoint for this study) fell to or below the level of detection (0.3 ng/mL) following DigiTab administration in all patients. Seven of 15 (47%) patients treated had complete resolution of digoxin toxicity by 4 h after DigiTab administration and 14 (93%) patients had complete resolution by 20 h. Ten patients (67%) showed improvement in their ECG within 4 h of DigiTab administration.

The results from the retrospective Study **PR007-CLN-rpt003** involving 14 patients corroborate efficacy and safety findings from the prospective DigiFab study of 15 patients (**TAb007-02**). For all efficacy endpoints, there was a progressively increasing rate of improvement over time across all patients with evaluable data. By the end of the 72 h post-treatment time interval, 100% (11/11) of evaluable patients demonstrated cardiac improvement, 100% (6/6) demonstrated improvement in gastrointestinal abnormalities, 88% (7/8) showed improvement in neurological abnormalities, general clinical disposition improved in 100% (9/9) of evaluable, and the rate of normalization of serum potassium levels was 86% (6/7). No patients demonstrated worsening of any efficacy endpoint during any time interval for which data were available after treatment.

These two independent studies were able to demonstrate that administration of DigiFab resulted in effective improvement in life-threatening digoxin toxicity in a majority of the patients treated. As the half-life of digoxin in patients with normal renal function is around 2 days, and even longer in patients with renal impairment, rapid reduction of digoxin concentrations, and resolution of digoxin toxicity, as demonstrated in the studies of DigiFab would not have been expected to occur spontaneously within 24 h, without the intervention of DigiFab. It is not possible to rule out that resolution of toxic effects was related to time (for example, metabolism and elimination of digoxin via biological processes) but this is a limitation inherent to uncontrolled, retrospective studies.

Despite a small number of patients and the limitations associated with the use of a historical control and with the conduct of a retrospective review, there were pharmacodynamic effects (reduction in serum free digoxin levels) and clinical responses that provided evidence of the

efficacy of DigiFab in the treatment of digoxin toxicity. However, efficacy of repeated dose of DigiFab was not evaluated adequately (only 1 patient in retrospective study PR007-CLN-rpt003 received 2 doses of DigiFab).

7. Clinical safety

7.1. Studies providing evaluable safety data

The following 3 studies provided evaluable safety data with DigiFab:

1. **TAb007-01**: a prospective, historically controlled, multicentre study of the safety, pharmacokinetics and pharmacodynamics of DigiFab in patients presenting with life-threatening digoxin toxicity. Patients in the historical control group were treated with Digibind.
2. **PR007-CLN-rpt003**: Multicenter Retrospective Review of the Clinical Efficacy and Safety of DigiFab in Digoxin Poisoned Patients.
3. **TAb007-02**: an open-label, parallel, randomised, pharmacokinetic and pharmacodynamic comparison between DigiFab and Digibind®, in healthy volunteers.

All patients and healthy subjects treated with DigiFab were evaluated for safety during hospitalisation and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate and temperature), ECG, clinical laboratory measures and interviews for subjective complaints. All patients and healthy subjects in the clinical trials of DigiFab were assessed for adverse events (AEs) while institutionalised or hospitalised. Follow-up visits were scheduled to assess any delayed or late adverse reactions to the study medication which may have presented after hospital discharge (except in the retrospective review study, PR007-CLN-rpt003). In the healthy subject Study **TAb007-02**, subjects were hospitalised for one day and follow-up visits were at 48 h, 7 days and 26 to 30 days after digoxin was administered. Digoxin toxic patients treated with DigiFab were assessed for AEs by direct observation during hospitalisation; patients in Study TAb007-01 were instructed to inform the study coordinator or the investigator of any AE that occurred after hospital discharge. During the 26 to 30 day follow-up visit, patients were asked about AEs in general. Safety was measured in the retrospective Study PR007-CLN-rpt003 as the total number of serious and non-serious drug-related AEs, the total number of drug-related AEs per patient and the rates of occurrence of specific drug-related AEs according to the patient records.

Integrated statistical analysis was not performed because the populations in the 3 studies were not similar. Descriptive statistics (number, percentage, mean, median, standard deviation and range) were calculated for all trials as applicable.

7.2. Pivotal studies that assessed safety as a primary outcome

None.

7.2.1. Clinical pharmacology studies

TAb007-02 compared PKs, PDs and safety of DigiFab with Digibind in healthy subjects.

7.3. Pivotal studies that assessed safety as a primary outcome

None.

7.4. Patient exposure

A total of 37 subjects have received DigiFab in clinical trials (8 healthy subjects and 29 patients with digitalis toxicity); 8 subjects received active comparator. All healthy subjects and all but one patient in the digoxin toxicity trials were treated with a single dose of DigiFab. One patient received a second dose of DigiFab in Study PR007-CLN-rpt003 (Table 8). The mean age of patients in the clinical studies was 64 to 71 years with majority (50-60%) being female; however, the study in healthy subjects had a younger population with mean age of 29 years (Table 9).

Table 8. Extent of exposure to DigiFab

Protocol	DigiFab Dose	No. Treated
TAb007-02 (Healthy subjects)	76 mg	8
TAb007-01 (Digoxin toxicity)	1-20 vials, 40-45 mg/vial	15
PR007-CLN-rpt001 (Retrospective review)	1-10* vials, 40mg/vial	14
Total number patients/subjects treated		37

* One patient received 7 vials as an initial dose with 3 further vials as a second dose.

Table 9. Demographic data

Demographic Parameters	TAb007-01	PR007-CLN-rpt003	TAb007-02	
	DigiFab n=15	DigiFab n=14	DigiFab n=8	Digibind n=8
Mean age, years (\pm SD)	64 (15)	71(14)	29 (4)	26 (2)
Age range, years	40-85	47-90	22-33	24-30
Mean body weight kg (\pm SD)	72 (20)	79.5 (20.1)	74 (9)	72 (7)
Mean height cm (\pm SD)	165 (9)	164.3 (14.6)	180 (7)	174 (6)
Gender:				
Male	6 (40%)	7(50%)	4 (50%)	4 (50%)
Female	9 (60%)	7(50%)	4 (50%)	4 (50%)

7.5. Adverse events

In the digoxin toxicity patient study **TAb007-01**, a total of 58 AEs were reported, including 30 (52%) events reported for a single patient. The remaining 28 AEs occurred in 11 patients, each experiencing 1 to 6 events. Most (43 of 58) AEs occurred in one patient each. Events reported in two patients included abdominal pain, constipation, nausea, worsening congestive heart failure, hypokalaemia and shortness of breath. Three patients had a urinary tract infection. Gastrointestinal events (19%), respiratory system events (12%), cardiovascular events (12%), metabolic and nutritional system events (10%), and whole body events (10%) were reported most often. Of these AEs, only 17 AEs were judged as remotely related to study drug. Ten of these events occurred in the same patient, including the three remotely related events deemed "severe" (intermittent pulmonary oedema, bilateral pleural effusion, and renal failure). The other remotely related events included seven moderate and seven mild intensity AEs. Most of these occurred on the day of infusion (3/17) or at two days after infusion (6/17). No AEs were deemed possibly, probably or definitely related to the use of DigiFab.

The incidence of AEs in this study appeared to be higher than that observed in the historical control patients treated with Digibind (Antman *et al*, 1990) who reported AEs in 32 of 150 patients (21%) treated with Digibind for digoxin toxicity (Table 10). In 14 (9%) of these patients, the reported AEs were judged possibly or probably caused by digoxin-specific Fab. Six patients rapidly developed hypokalaemia. Four patients experienced exacerbation of congestive heart failure (possibly due to loss of inotropic support from digitalis therapy). Two patients

suffered mild hypotensive episodes (each had been haemodynamically unstable before Fab infusion), one patient complained of nausea after Fab treatment (although nausea was also present before treatment), and one neonate patient, several h old, developed transient apnoea during infusion. Overall, 43 patients did not survive to hospital discharge in the Antman study. The majority of deaths were ascribed to underlying heart disease still present after resolution of digitalis toxicity. While the authors reported 32 AEs in this trial, there were 43 deaths which were not reported as AEs and this may have contributed to the apparent differences in AE incidences between the Digibind and DigiFab studies.

Hickey *et al.* (1991) reported AEs in 215 of 717 patients treated with Digibind for digoxin toxicity (30%). In 52 (7%) of these patients, the reported AEs were judged possibly or probably caused by digoxin-specific Fab. The published study lacks details to account for all of these adverse events. However, it was reported that six patients developed allergic reactions (two with pruritic rash; one with pruritic rash, facial swelling and flushing; one with urticaria; one with thrombocytopenia; and one with shaking and chills but no fever). Two other patients experienced fever and dyspnoea but these were attributed to underlying conditions and not to Fab. A total of 171 patients were reported to have died in the Hickey study; none of the deaths were attributed to Fab. Eighty-six deaths occurred within two days and 142 occurred within three weeks after Fab treatment.

Table 10. Adverse events in TAB007-01 compared to published literature

Adverse Events	DigiFab (n=15)	Hickey Study ⁷ (n=717)	Antman Study ⁶ (n=150)
Total No. Patients with Adverse Events	12 (80%)	215 (30%)	32 (21%)
Total No. Patients with Study Drug Related Events	6 (40%)	52 (7%)	Not Reported 14 (9%)
Total No. Adverse Events	58	Not Reported	Not Reported
Total No. Deaths	1 (7%)	171 (24%)	43 (29%)

In the retrospective Study **PR007-CLN-rpt003**, a total of 14 AEs were identified in the medical records of 10 patients that manifested during and/or up to 72 h after the initiation of DigiFab treatment. Only 2 (14%) events were judged from the patient medical records as related to the study drug; both were cardiovascular disorders (hypotension, severe; tachycardia, moderate). Cardiovascular events were most common (5/14, 36%), followed by gastrointestinal events (3/14, 21%) and neurological events (3/14, 21%), respiratory events (2/14, 14%) and skin/general events (1/14, 7%). The majority of non-serious AEs were of moderate (6/14, 43%) or mild (5/14, 36%) intensity. Only one (7%) non-serious AE was of severe intensity (Table 11). No formal analyses of AEs were performed due to small sample size in this study and the relatively low frequency of AEs reported. Half (7) of the AEs reported in this study were present only during the final post-treat interval (>24 to 72 h after treatment). Only one AE manifested during treatment (hypotension), but was resolved by the end of treatment. One AE (bronchospasm) manifested within 0 to 4 h after treatment and persisted until the final post-treatment interval. Four AEs were present during only the >4 to 12 h (1) or >12 to 24 h (3) post-treatment interval. The timing and duration for one AE (anorexia) was unknown, but the event resolved prior to discharge. Three (21%) AEs were treated by intravenous administration of normal saline, one (7%) AE was treated with albuterol, one with digitalis disimpaction (7%), and one (7%) with supportive care ("comfort measures"). No medication or special measures were used to treat the remaining six (50%) AEs. All AEs were documented as resolved by the end of the patient's hospital stay, with the exception of one (anxiety: moderate, unrelated, on-going).

Table 11. Frequencies (%) of AEs by intensity and relatedness for Study PR007-CLN-rpt003

Body System Adverse Event	Mild		Moderate		Severe		Total		Total
	Related †	NR	Related †	NR	Related †	NR	Related †	NR	R + NR
Cardiovascular									
Cardiac Arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)
Hypotension	0 (0)	1 (7)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)	2 (14)
Tachycardia	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	1 (7)	1 (7)	2 (14)
TOTAL	0 (0)	1 (7)	1 (7)	1 (7)	1 (7)	1 (7)	2 (14)	3 (21)	5 (36)
Gastrointestinal									
Abdominal Pain	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Anorexia	0 (0)	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	2 (14)	2 (14)
TOTAL	0 (0)	1 (7)	0 (0)	2 (14)	0 (0)	0 (0)	0 (0)	3 (21)	3 (21)
Neurological									
Anxiety	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Fatigue	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Pre-syncope	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	2 (14)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	3 (21)	3 (21)
Respiratory									
Bronchospasm	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Respiratory	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)
Failure	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	0 (0)	2 (14)	2 (14)
TOTAL	0 (0)	0 (0)	0 (0)	2 (14)	0 (0)	2 (14)	0 (0)	4 (28)	4 (28)
Skin/General									
Fever	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	5 (36)	1 (7)	5 (36)	1 (7)	2 (14)	2 (14)	12 (86)	14 (100)

†Related = definitely or possibly related to DigiFab therapy

A total of 24 AEs were reported in Study **Tab007-02** in healthy subjects; these included 15 events reported by six subjects in the DigiFab group and nine events reported by five subjects in the Digibind group (Table 12). Many of the events were due to intravenous digoxin infusions and general disorders (influenza symptoms and tiredness). AEs that may have been associated with the Fab infusions included brief nausea during a Digibind infusion and hypotension 5 h after a DigiFab infusion. The number of AEs in both treatment groups was considered low and no events considered severe in intensity occurred.

Table 12. Summary of AEs listed according to the World Health Organization Classification for Study Tab007-02

ADVERSE EVENT		Total number of events recorded (number of subjects reporting)			
Body System	Adverse Event	DigiFab	Causality	Digibind	Causality
Application Site Disorders	Burning sensation at the infusion site	2 (2)	A*	-	-
	Pain at the infusion site	1 (1)	A*	1 (1)	A
	Pain left lower arm	2 (2)	A*	-	-
	Redness of left lower arm	1 (1)	A*	-	-
Gastro-Intestinal System Disorders	Diarrhoea	1 (1)	NA	-	-
	Bloating	1 (1)	U	-	-
	Nausea	-	-	1 (1)	A
	Toothache	-	-	1 (1)	NA
Central and Peripheral Nervous System Disorders	Headache	1 (1)	NA	2 (2)	**
Body as a Whole - General Disorders	Influenza like symptoms	2 (2)	NA	2 (2)	NA
	Tiredness	1 (1)	U	1 (1)	U
Vascular (Extracardiac) Disorders	Phlebitis of infusion vein	1 (1)	-	-	-
Skin and Appendages Disorders	Skin dry	-	-	1 (1)	U
Autonomic Nervous System Disorders	Hypotension postural	2 (1)	A	-	-
Total		15 (6)		9 (5)	

*associated with digoxin infusion

**one event was considered not associated, while the second event was considered associated with digoxin infusion.

A = associated; NA = not associated; U = unknown

7.5.1. Common AEs

None of the adverse events reported were common. The number of patients treated in clinical trials do not allow for a meaningful calculation of the frequency of AEs. AEs that were reported by more than one patient included abdominal pain, hypotension, nausea, hypokalaemia, chest

pain and dyspnoea. The most common AEs listed by body system in the 3 clinical studies were Cardiovascular (18%), gastrointestinal (16%), respiratory (12%) and 'body as a whole' AEs.

7.5.2. Acute hypersensitivity

In Study **TA007-02**, healthy subjects treated with DigiFab or Digibind experienced no anaphylactic or anaphylactoid reactions⁸. There were five AEs that occurred acutely, within 24 h of administration of study drug and all were classified as mild or moderate intensity.

None of the patients in the digoxin toxicity study (**TA007-01**) experienced anaphylactic or anaphylactoid reactions to DigiFab. Of the remotely related events, two patients experienced three events, which occurred on the same day as DigiFab administration, although it is not known how long post infusion the events occurred. One patient experienced both moderate intermittent hypokalaemia and moderate intermittent electrolyte imbalance. The other patient experienced mild hypokalaemia. All three events are expected clinical situations with reversal of digoxin toxicity.

In the retrospective Study **PR007-CLN-rpt003**, the records did not reveal any reports of anaphylactic or anaphylactoid reactions to DigiFab. Two patients experienced AEs on the same day as DigiFab administration that could potentially have been acute hypersensitivity reactions to DigiFab. One patient experienced bronchospasm in the 0 to 4 h post-treatment period. This was considered unrelated to treatment. The other patient experienced hypotension during treatment, which was considered possibly related to treatment.

In the historical control patients treated with Digibind, Antman *et al.*(1990) reported that six patients rapidly developed hypokalaemia. Four patients experienced exacerbation of congestive heart failure (possibly due to loss of inotropic support from digitalis therapy, although the temporal relationship is not reported). Two patients suffered mild hypotensive episodes (each had been haemodynamically unstable before Fab infusion and the temporal relationship is not reported). One patient complained of nausea after Fab treatment (although nausea was also present before treatment) and one neonatal patient, several h old, developed transient apnoea during infusion. Hickey *et al.*(1991) reported that six patients developed allergic reactions (two with pruritic rash; one with pruritic rash, facial swelling and flushing; one with urticaria; one with thrombocytopenia; and one with rigors but no fever). Two other patients experienced fever and dyspnoea but these were attributed to underlying conditions and not to Fab. The temporal relationship to Digibind was not described.

7.5.3. Deaths and other serious adverse events

A total of three patient deaths were recorded in the patient studies. There was one patient death in Study **TA007-01** when a patient died of lung cancer during the follow up period and this death was considered unrelated to treatment with DigiFab. There were two deaths reported in Study **PR007-CLN-rpt003**. Both occurred more than five days after the end of DigiFab therapy and as a result of complications from underlying medical conditions⁹.

Deaths are not uncommon in patients with digoxin toxicity and deaths were reported in the historical control studies for TA007-01, including 43/150 (29%) patients in the Antman study and 171/717 (24%) in the Hickey study. Antman *et al.*(1990) ascribed the majority of deaths to underlying heart disease still present after resolution of digitalis toxicity. In the Hickey study, 86 deaths occurred within 2 days of Fab treatment and the remaining 142 within 3 weeks; none was attributed to Fab. The median serum digoxin concentration in the Antman study was 8.0

⁸ Early reactions might include anaphylactic reactions, occurring within seconds or minutes of drug administration, and anaphylactoid reactions, which are milder and slower in onset (15 to 20 minutes) and begin during the time frame of dose administration through peak plasma concentration (2 h).

⁹ [information redacted] died from respiratory failure secondary to overwhelming sepsis; [information redacted] died from cardiac arrest secondary to lung cancer. Both SAEs were judged as unrelated to DigiFab therapy.

ng/ml compared to only 5.0 ng/ml in the DigiFab treated patients (TAb007-01), indicating a more severely toxic group of patients in the Antman study.

In the digoxin toxicity study (**TAb007-01**), 4 patients experienced a total of 5 serious adverse events (SAEs). Four SAEs that occurred in 3 patients were pulmonary oedema, palpitations and dyspnoea, congestive heart failure and angina and these were categorised as serious because hospitalisation or prolonged hospitalisation was required. Causality was difficult to assess in these 3 patients because they had been taking digoxin therapeutically (1 for congestive heart failure and 2 for atrial fibrillation), all 3 patients had a significant cardiac history and were of advanced age (67 years, 77 years and 82 years).

In Study **PR007-CLN-rpt003**, other than the two SAEs that resulted in death (see above), there were no recorded SAEs

No SAEs or deaths were reported in the healthy subject trial (**TAb007-02**).

7.5.4. Discontinuation due to adverse events

No patients discontinued study participation due to an adverse event.

7.5.5. Laboratory tests, vital signs, ECG

Clinical laboratory assessments and human anti-sheep antibody (HASA) response were evaluated in the healthy subjects and some patients treated with DigiFab.

In the healthy subject study (**TAb007-02**), no differences could be detected in laboratory values in subjects treated with DigiFab compared to Digibind. There was no effect on any laboratory safety parameter during the study that was definitely related to drug administration. There were no clinically or statistically significant changes in haematology, serum chemistry and electrolytes, urinalysis or creatinine clearance. None of the 16 subjects demonstrated a detectable HASA response 26 to 30 days post treatment.

In the digoxin toxicity patient study (TAb007-01) average concentrations for most analytes measured during 24 h after treatment were within the normal range. There were no trends or clinically unexpected changes in serum electrolytes or other laboratory measures. Besides digoxin concentrations, a total of 48 abnormal laboratory values were deemed “clinically significant” by the investigator and included potassium, glucose, blood urea nitrogen (BUN) and creatinine. These reflected either a digoxin effect on potassium (21%) or another underlying clinical condition [diabetes (8%), renal insufficiency (48%) or dehydration (10%)]. Fifty four percent of the clinically significant values (26 of 48 events) were present at baseline and 15 (31%) of the values were continuing abnormalities from baseline.

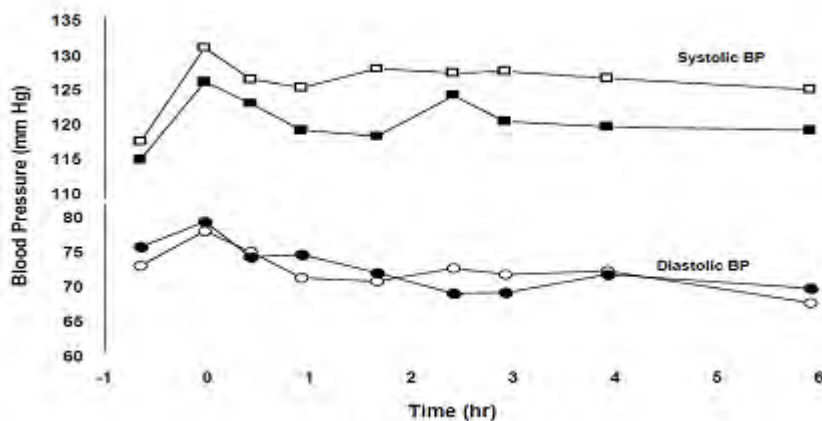
Mean potassium values appear slightly higher at baseline and at 0.5 and 1 h when compared to the later timepoints; no formal statistical tests were applied due to the small number of subjects. Only four of the 15 patients presented with serum potassium concentrations outside or at the upper end of the normal range. Values decreased by 1 h post DigiFab dose (there was concomitant administration of potassium chloride in 2 of these 4 patients). Effects on other laboratory values were not consistent and no other noteworthy trends were observed.

In the retrospective study (PR007-CLN-rpt003), no safety-related laboratory tests were required to be collected or analysed as part of this retrospective study. The only laboratory measurements that were collected before and after treatment from the medical record (as available) were serum potassium levels and serum creatinine. Serum creatinine levels at baseline for 11/13 (43%) patients were abnormal, suggesting abnormal renal function. By the final post-treatment time interval, 4/11 (36%) still had abnormal creatinine levels. No measurements for any patient are suggestive of safety concerns related to treatment. The normalisation in potassium levels was achieved in some patients within the first four h after treatment with DigiFab, and by 72 h post-treatment the rate was 86% (6/7).

Systolic and diastolic blood pressure, heart rate, respiration and temperature were evaluated in TAb007-01 and **TA007-02**. In the healthy subject population (Study TAb009-02), no permanent changes in vital signs were observed. The systolic and diastolic blood pressure increased in both groups after starting the digoxin infusion, but then remained stable throughout the study period (Figure 5).

Figure 5. Supine systolic and diastolic blood pressure in the DigiFab Groups

(Solid Symbols) and Digibind Group (Open Symbols) - Study TAb007-02



Results are average values in each group. \pm SEM.

In the digoxin toxicity Study TAb007-01, changes in vital signs are expected to be reflective of the cardiac glycoside poisoning at entry into the trial with resolution of the abnormalities as the patient is treated with DigiFab and the glycoside toxicity subsides. Mean values for systolic and diastolic blood pressure appeared to decrease from baseline over 24 h (Figure 6) and mean values for pulse rate indicated a slight, but consistent increase, as expected over time (Figure 7).

Figure 6. Mean (SD) systolic and diastolic blood pressure after DigiFab administration (TA007-01)

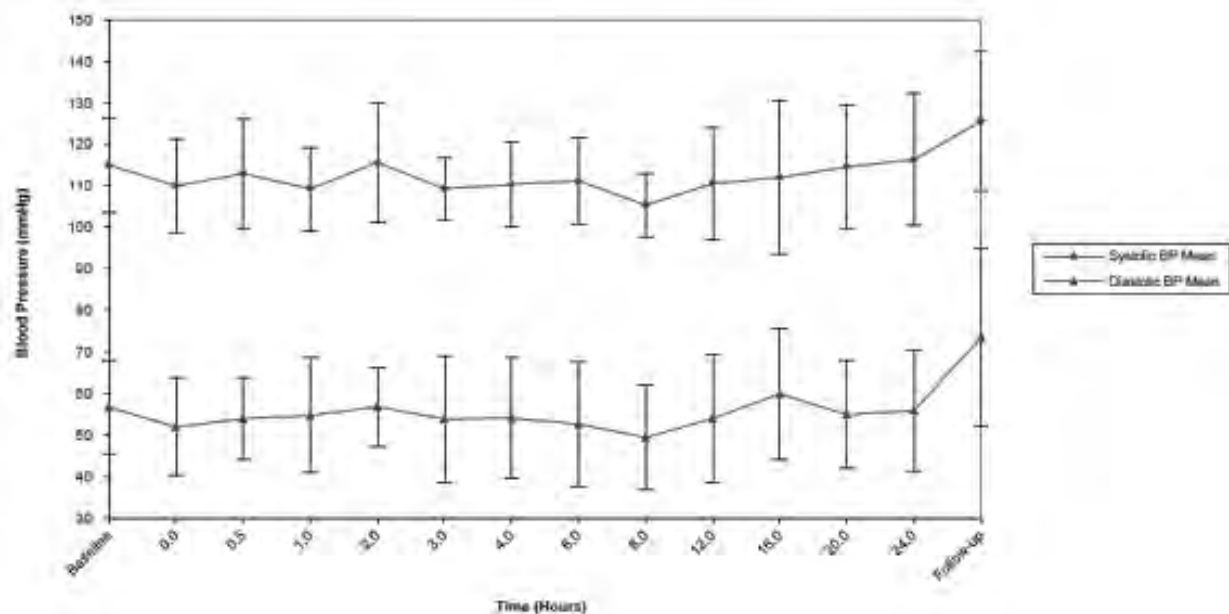
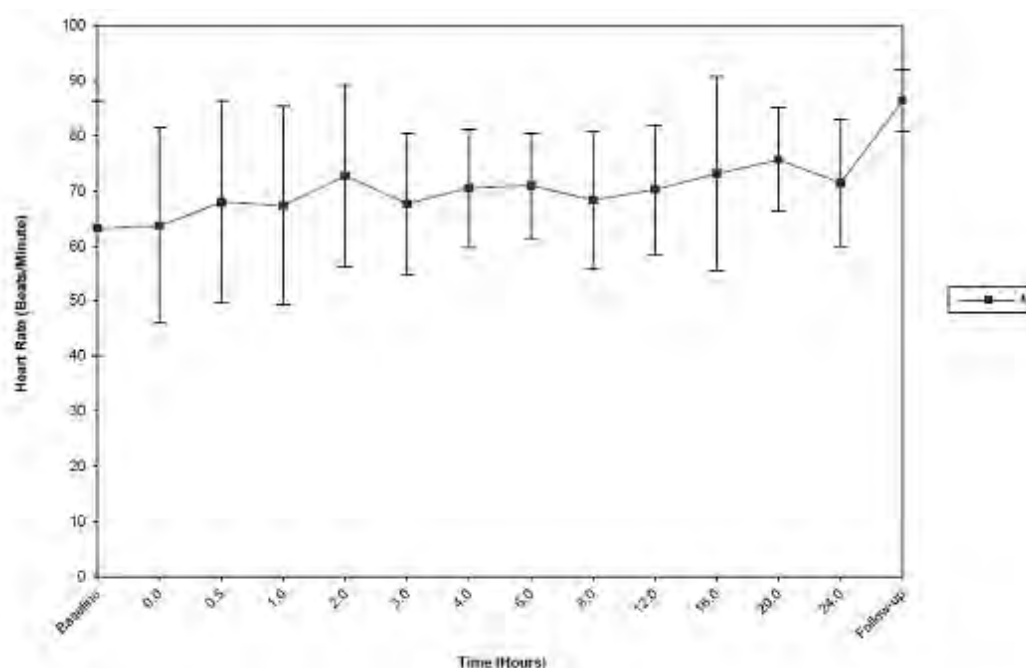


Figure 7. Mean (SD) Heart Rate after DigiFab Administration (TAb007-01)

For all trials, there were no abnormal physical examination findings other than those consistent with digoxin toxicity (for example, nausea, visual disturbances, somnolence). Healthy subjects reported findings such as digoxin infusion-related phlebitis or redness.

In the healthy subject group, there were no clinically or statistically significant changes in ventricular rate, P-wave duration, PQ interval, QRS interval or QTc interval. However, the mean values of QTc intervals were slightly shorter after digoxin dosing compared to pre-dose values and to values after Digibind and DigiFab treatment. As expected, baseline ECG results were abnormal for patients with digoxin poisoning in Studies TAb007-01 and PR007-CLN-rpt003.

7.6. Postmarketing experience

DigiFab has been marketed and used in patients in the USA since February 2002. Recently, DigiFab was also approved in the UK, Canada and Switzerland. Between February 2002 and 31 August 2011, 299,319 vials of DigiFab were sold globally. It is not possible to determine the number of patients treated or the doses received, but an estimate based on the average dose (4 vials) used in the DigiFab study (TAb007-01) would indicate 74,830 patients received DigiFab during that time. There have been five (5) spontaneous cases up to the 31 August 2011 and all of the events involved cases of digoxin toxicity and elevated digoxin levels. The reporters' assessments of these cases were based solely on the fact that serum digoxin concentrations did not respond as expected. Additional clinical information related to these patients was unavailable despite attempts to obtain it. It was not possible to confirm potency of the DigiFab preparations with the exception of once case (this batch of DigiFab was found to pass specification). No further action was taken regarding these events and these events were not considered to be indicative of an adverse trend in relation to DigiFab product quality.

This additional post-marketing evidence supports the relative safety of DigiFab, although the applicant acknowledges that adverse drug reactions (ADRs) are underreported and the acute nature of treatment with DigiFab makes it difficult to identify ADRs, particularly if hypersensitivity is delayed.

On [information redacted], 2013, there was a spontaneous serious adverse event was received from a nurse concerning death of a [information redacted] due to digoxin toxicity. The actual

event occurred in [information redacted]. Based on review of the limited information provided by the sponsor for this case, it is very difficult to rule out any relationship between lack of efficacy of DigiFab and death due to digoxin toxicity in this patient. However, interpretation is limited by lack of information on the actual digoxin-specific Fab used in this patient, dose and time of administration.

On [information redacted], 2013, there was a report of death from toxic digoxin levels/Digoxin level was higher (8.1 µg/L) [Drug effect decreased]. This spontaneous adverse event was received from a pharmacist concerning a patient, age and gender not reported. The patient's medical history included atrial fibrillation from an unspecified date, for which digoxin was given. According to the lab results, there was slight reduction in digoxin levels following administration of DigiFab, but these were again raised to toxic levels (8.1 µg/ml) before death of the patient. It is very difficult to rule out any relationship between lack of efficacy of DigiFab and death due to digoxin toxicity in this patient. However, there is very limited data available case including confirmed digoxin levels and dose and timing of digoxin immune Fab administration with relation to digoxin toxicity.

During the course of this evaluation, there was a report of a SAE (death of a [information redacted]) on [information redacted]. Review of the report suggested that the death which occurred 5 days following administration of DigiFab was due to fatal acute kidney injury, dehydration, chronic heart failure, ischaemic heart disease (IHD) and anaemia to be unrelated to DigiFab. Following review of limited data available, it appears that this case report does not modify the risk benefit balance of DigiFab.

Comments: Overall, review of the above 3 spontaneous reports of deaths suggest that cause of death may have been related to lack of efficacy of DigiFab. However, interpretation is limited by lack of adequate data especially regarding temporal relationships and inadequate information on serum digoxin levels.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

None.

7.7.2. Haematological toxicity

None.

7.7.3. Serious skin reactions

None.

7.7.4. Cardiovascular safety

The incidence of CV AEs was high but this would be expected considering the nature of the disease being treated.

7.7.5. Unwanted immunological events

There were no reports of anaphylactic or anaphylactoid reactions in the 3 clinical studies provided in this submission.

However, all patients should be informed of the possibility of an anaphylactic reaction and when receiving DigiFab should be carefully monitored for signs and symptoms of an acute allergic reaction (such as urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal oedema, hypotension, tachycardia) and treated immediately with appropriate emergency medical care (such as oxygen, diphenhydramine, corticosteroids, volume expansion and airway management). If an anaphylactic reaction occurs during the infusion, DigiFab administration should be terminated at once and appropriate treatment

administered. The need for adrenaline should be balanced against its potential risk in the setting of digoxin toxicity. Patients with known allergies to sheep protein would be particularly at risk for an anaphylactic reaction, as would individuals who have previously received intact ovine antibodies or ovine Fab. Following discharge from the hospital, patients should be advised to contact their physician immediately if they experience any signs and symptoms of delayed allergic reactions or serum sickness (such as rash, pruritus and urticaria) after hospital discharge. Prior treatment with digoxin-specific ovine immune Fab carries a theoretical risk of sensitization to ovine serum protein and possible diminution of the efficacy of the drug due to the presence of human antibodies against ovine Fab.

All the above facts have been adequately covered in the proposed PI for DigiFab.

7.8. Other safety issues

7.8.1. Safety in special populations

There are no data relating to individualising therapy on the basis of intrinsic or extrinsic factors.

Pregnancy/lactation: Studies of animal carcinogenicity and reproduction have not been conducted with DigiFab. It is also not known whether DigiFab can harm the foetus when administered to a pregnant woman or whether it can affect reproduction capacity. DigiFab should be given to a pregnant woman only if the potential benefit is considered to outweigh the unknown potential risks. It is not known whether DigiFab is excreted in human breast milk but because many drugs are excreted in human milk, caution should be exercised when DigiFab is administered to a woman who is breast feeding.

Elderly patients: Specific studies in elderly patients have not been conducted. Of the 29 patients given DigiFab in clinical studies the average age was 67 years, and over half of the patients (19/29) were 65 years of age or older. The oldest patient in the studies was 90 years old. There is no evidence that the efficacy of DigiFab would be altered due to advanced age alone, however elderly patients have a higher chance of having impaired renal function and therefore should be monitored more closely for recurrent toxicity.

Paediatric patients: Specific studies in paediatric patients have not been conducted and no paediatric patients were enrolled in the clinical studies of DigiFab. However, it is relevant to note that Digibind has been used successfully to treat infants. As with all drugs, the use of DigiFab in infants and children should be based on careful consideration of the benefits compared with the potential risks.

Renal impairment: Although a specific study of the efficacy and safety of DigiFab in renally impaired patients was not undertaken, a total of 20 patients in both TAB007-01 and PR007-CLN-rpt003 had renal impairment as evidenced by elevated serum creatinine levels (range 1.2 to 8.6 mg/mL). The elimination half-life of DigiFab in renal failure has not been clearly defined, although patients with renal dysfunction have been successfully treated with Digibind. Although there is no conclusive evidence to suggest that the time-course of therapeutic effect is any different in these patients than in patients with normal renal function, excretion of the Fab fragment-digoxin complex from the body is probably delayed. There is one case report of recurrence of atrioventricular block due to digoxin in a functionally anephric patient 10 days after its initial reversal by ovine Fab therapy¹⁷. This clinical event persisted for more than a week. In patients that are functionally anephric, failure to clear the Fab-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated. It is uncertain whether the failure to eliminate the Fab-digoxin complex in severe renal impairment may lead to re-intoxication with digoxin following the release of previously bound digoxin into the blood. However, patients with severe renal failure who receive DigiFab for digoxin toxicity should be monitored for a prolonged period for possible recurrence of toxicity.

7.9. Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not specifically evaluated in the studies. Concomitant medications are discussed for each of the study populations.

In Study **TA007-02**, the healthy subjects were not permitted to take any prescription medications, with the exception of oral contraceptives and antibiotics. No non-permitted medications were taken during the period of study drug infusion.

In the Digoxin Toxicity Patient Study (TA007-01), most patients were receiving cardiovascular agents on enrolment and throughout the trial. Medications administered during the trial reflect the clinical conditions of individual patients (Table 13).

Table 13. Percent of patients administered various medications by WHO-ATC system class

System Class	Medication History	Concomitant Medication
Alimentary tract and metabolism	93%	93%
Blood and blood forming organs	53%	73%
Cardiovascular system	93%	80%
Genito urinary system and sex hormones	27%	33%
Nervous system	87%	80%
Respiratory system	7%	40%

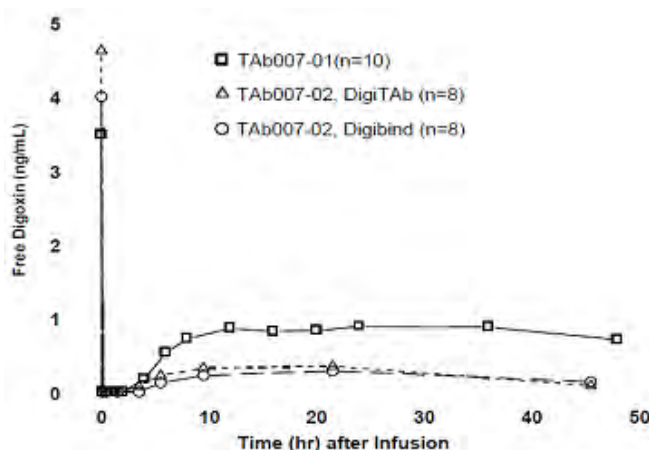
In the retrospective study (PR007-CLN-rpt003), the included patients were given a wide range of concomitant therapies. There was no particular therapy given before, during, or after DigiFab was administered to any patient that appeared to have a confounding effect on response. Similarly, there were no apparent relationships between past or concurrent illnesses and response.

7.10. Other safety issues- overdose, withdrawal and rebound

The maximum amount of DigiFab that can safely be administered in single or multiple doses has not been determined. Doses ranging from 1 to 20 vials (40 to 800 mg) have been safely administered in controlled clinical trials of DigiFab.

In clinical studies, DigiFab reduced free digoxin concentrations to below the level of quantitation at the end of the Fab infusion (Figure 8). In the healthy subject study (**TA007-02**) there was a slight rebound of free digoxin between 8 and 24 h post-Fab dosing (mean peak concentrations of 0.5 ± 0.1 ng/mL for both treatment groups). There do not appear to be any differences between the DigiFab and Digibind groups in Study **TA007-02** with respect to rebound.

Figure 8. Serum free digoxin concentration versus time TA007-01 and TA007-02



In the patient study (**TA007-01**), all patients maintained free serum digoxin concentrations at or less than 0.3 ng/mL for an average of 9.6 h after Fab infusion (range: 4.5 to 24.5 h). The maximum rebound free digoxin concentration averaged 1.4 ± 0.8 ng/mL and ranged from 0.3 to 2.8 ng/mL. The time to maximum free serum digoxin rebound averaged 15.1 h (range 6.5 to 36.5 h).

Comments: Rebound increase in serum free digoxin concentrations have previously been demonstrated following Digibind use. There do not appear to be any differences between the DigiFab and Digibind groups in Study TA007-02 with respect to rebound. Historical data with Digibind shows that the average maximum rebound free digoxin concentration was 1.7 ± 1.3 mmol/mL (1.3 ± 1.0 ng/mL) and is consistent with the DigiFab data. The time to maximum free digoxin rebound from published historical data for patients without severe renal impairment treated with Digibind ranged from 3.5 to 24 h with an average of 11 ± 5.6 h, which is consistent with the DigiFab data.

7.11. Evaluator's overall conclusions on clinical safety

All patients and healthy subjects treated with DigiFab were evaluated for safety during hospitalisation and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate, and temperature), ECG, clinical laboratory measures and interviews for subjective complaints. A total of 37 subjects or patients have received DigiFab in clinical studies (TA007-01, TA007-02 and PR007-CLN-rpt 003. Doses of DigiFab ranged from 76 mg in the healthy subject study (N = 8) up to 800 mg (20 vials; average dose 160 mg or 4 vials) in the patient studies (N = 29). All healthy subjects, and all except one patient in the digoxin toxicity studies, were treated with a single dose of DigiFab. One patient in study PR007-CLN-rpt 001 received two doses of DigiFab.

In the clinical studies of DigiFab, 6 of 15 patients in the digoxin overdose study (TA007-01) had a total of 17 AEs, most were mild to moderate in nature and all were deemed only "remotely associated" with DigiFab. Three events were deemed "severe", all occurred in one patient and consisted of the following: pulmonary oedema, bilateral pleural effusion and renal failure. After reviewing the case, it was determined that these events were likely due to the loss of digoxin inotropic support in combination with the patient's underlying medical condition. The remaining 41 AEs that occurred during the study were deemed "not associated" with DigiFab. In Sstudy PR007-CLN-rpt003 a total of 14 AEs were identified in 10 patients during and/or up to 72 h after the initiation of treatment. Two serious AEs (SAEs) were reported (cardiac arrest and respiratory failure), both of which were judged to be unrelated to DigiFab therapy. Only two (14%) events were deemed as related to the study drug; both were cardiovascular disorders (hypotension, severe; tachycardia, moderate).

Of 8 healthy subjects who received DigiFab in Study TA007-02, only 2 experienced an AE that was considered to be associated with DigiFab. The reactions were 1 episode of phlebitis of the infusion vein and 1 episode of moderate postural hypotension, which became mild prior to resolving. In all 3 clinical studies, the patients (or healthy subjects in Study TA007-01) experienced no anaphylactic or anaphylactoid reactions.

Rebound of serum free digoxin levels is unlikely to be of significant clinical consequence in patients with normal renal function, however there is one case report of recurrence of atrioventricular block due to digoxin in a functionally anephric patient 10 days after its initial reversal by DigiFab therapy. This clinical event persisted for more than a week. Failure to clear the Fab-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated in anephric patients. It is uncertain whether the failure to eliminate the Fab-digoxin complex in severe renal impairment may lead to re-intoxication with digoxin following the release of previously bound digoxin into the blood. However, patients with severe renal failure who receive DigiFab for digoxin toxicity should be monitored for a prolonged period for

possible recurrence of toxicity. Monitoring of free (unbound) digoxin concentrations after the administration may be appropriate in order to establish recrudescence toxicity in renal failure patients. The above facts have been adequately addressed in the proposed PI for DigiFab.

Based on experience with the highly similar product Digibind, the following adverse reactions could occur with the use of DigiFab: Exacerbation of low cardiac output states and congestive heart failure due to the withdrawal of inotropic effect of digitalis; Hypokalaemia due to reactivation of the sodium-potassium ATPase; Rapid ventricular response in patients with atrial fibrillation due to withdrawal of the effects of digitalis on the atrioventricular node; rare allergic reactions. These have been adequately mentioned in proposed PI and Consumer Medicines Information (CMI) for DigiFab.

Clinical laboratory data support the safety of DigiFab. No clinically or statistically significant abnormal laboratory values were attributed to DigiFab in the clinical studies undertaken (although only creatinine and potassium levels were recorded from the retrospective review study). No Human Anti-Sheep Antibody (HASA) response was observed in any of the patients or subjects tested.

Across studies, no DigiFab infusion was terminated due to an AE, nor were there any DigiFab related deaths. There was one unrelated death and three other patients who experienced 4 serious AEs in the study TAb007-01. None of these serious adverse events (SAEs) were considered related to DigiFab but were considered to be related to the underlying cardiac condition of the patient and due to withdrawal of inotropic support of digoxin.

Although it is recognised that there are difficulties deriving meaningful and definitive conclusions on safety based on the size and nature of the studies conducted, it is apparent that DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an AE that was considered possibly, probably or definitely related to DigiFab. In comparison, historical data on Digibind in the studies reported by Antman (1990) and Hickey (1991) showed that 7 to 9% of patients experienced an AE considered possibly or probably related to Digibind. The AE profile was similar to that of Digibind in the study of healthy subjects.

DigiFab has been marketed and used in patients in the USA since February 2002. More recently DigiFab was also approved in the UK, Canada and Switzerland [information redacted] and it is estimated that 74,830 patients received DigiFab during that time. The post-marketing evidence supports the relative safety of DigiFab, although the applicant acknowledges that adverse drug reactions (ADRs) are underreported and the acute nature of treatment with DigiFab makes it difficult to identify ADRs, particularly if hypersensitivity is delayed. Finally, a patient registry is currently underway in the UK to collect additional information on safety and immunogenicity associated with the use of DigiFab. As no subjects under 18 years of age, pregnant or lactating women, patients with hepatic impairment, patients with previous pacemaker insertion or who have been treated with a previous dose of digoxin immune Fab were included in the DigiFab studies, the safety of these populations will be followed closely through routine post-approval pharmacovigilance.

Safety of repeated dose of DigiFab was not evaluated adequately (only 1 patient in retrospective study PR007-CLN-rpt003 received 2 doses of DigiFab).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of DigiFab in the proposed usage are:

- Despite a small number of patients and the limitations associated with the use of a historical control and with the conduct of a retrospective review in the 2 clinical studies (TAb007-02 and PR007-CLN-rpt 003), there were pharmacodynamic effects (reduction in serum free digoxin levels) and clinical responses that provided evidence of the efficacy of DigiFab in the treatment of digoxin toxicity.
- DigiTab (DigiFab) was shown to bind digoxin in a manner equivalent to Digibind, reducing serum free digoxin levels to below 0.3ng/ml (lower limit of quantification (LOQ)) in all treated healthy subjects (TAb007-02).
- DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an AE that was considered possibly, probably or definitely related to DigiFab.
- Following withdrawal in 2012 of the only other digoxin antibody preparation (Digibind from GSK) available in Australia, DigiFab would help to provide supply of a potentially life-saving product for the treatment of digoxin poisoning for the Australian population.

8.2. First round assessment of risks

The risks of DigiFab in the proposed usage are:

- Comparison with historical data (Study TAb007-01) presents some difficulties in interpretation of efficacy and safety of DigiFab, as does a retrospective review (PR007-CLN-rpt003).
- Of the 29 patients evaluated in the 2 clinical DigiFab studies, majority had chronic digitalis poisoning. Efficacy/ safety of DigiFab were not evaluated adequately in patients with acute digoxin toxicity.
- Efficacy and safety was only evaluated following a single dose of DigiFab (only 1 patient in retrospective Study PR007-CLN-rpt003 received 2 doses of DigiFab).
- The number of patients evaluated is much below recommended guidelines for a new chemical entity (NCE) although it is acknowledged that digoxin toxicity is rare and the emergency nature of the proposed indication makes recruiting patients into trials difficult.
- The possible adverse reactions produced by the administration of heterologous animal proteins to humans include anaphylactic and anaphylactoid reactions, delayed allergic reactions and a possible febrile response to immune complexes formed by animal antibodies. Although no patient in the clinical studies of DigiFab has experienced a severe anaphylactic reaction, the possibility of an anaphylactic reaction cannot be ruled out and should be considered.

8.3. First round assessment of benefit-risk balance

Life-threatening digoxin toxicity is not common and, as such, DigiFab has been designated an orphan medicinal product in Australia whereby the prevalence of the condition must be less than 2000 patients. It is acknowledged that the clinical data set is limited compared with the current expectations for a stand-alone marketing authorisation application but this is a result of the emergency nature and the rare prevalence of the condition. The nature of the condition severely restricted the ability to recruit adequate numbers of subjects in order to pursue formal randomised, controlled trials.

Antibody preparations in the treatment of digoxin toxicity have been available for over twenty years. The majority of literature reports on the efficacy and safety of digoxin toxicity antibody therapy relate to Digibind, as this was the first digoxin-specific Fab product approved in the UK

(1985), USA (1986) and Australia (1991). Although authorisation of DigiFab is not being sought on a biosimilar basis, demonstration of equivalent digoxin binding capacity of DigiFab with already approved DigiBind would still be relevant to the demonstration of efficacy for DigiFab. Furthermore, evidence for efficacy of DigiFab is provided from the clinical studies in terms of binding of DigiFab to digoxin (measured as free and total digoxin concentrations), together with clinical evidence (ECG changes, clinical sequelae) of concomitant loss of glycoside effects.

Although it is acknowledged that comparison with historical data presents some difficulties, as does a retrospective review and patient numbers were limited due to the nature of the condition, these two independent studies were able to demonstrate that administration of DigiFab resulted in effective improvement in life-threatening digoxin toxicity in a majority of the patients treated.

DigiFab® has very recently been granted approval under Section 19A of the Therapeutic Goods Act 1989, for the importation and supply of this unregistered therapeutic good due to the forthcoming unavailability of a similar currently registered therapeutic good in Australia. [information redacted]

Although it is recognised that there are difficulties deriving meaningful and definitive conclusions on safety based on the size and nature of the studies conducted, it is apparent that DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an adverse event that was considered possibly, probably or definitely related to DigiFab.

In conclusion, for patients with serious digoxin toxicity, immunotherapy with digoxin specific Fab is still the treatment of choice. DigiFab successfully reduces free digoxin concentrations, which is the primary efficacy endpoint for demonstration of efficacy. Although the clinical studies were small due to the rarity and nature of the condition and there were limitations associated with a comparison against a historical control and with a retrospective review, free digoxin concentrations were shown to be reduced by DigiFab, where it was possible to measure this parameter. In addition, DigiFab was effective in reversing the signs and symptoms of digoxin toxicity in patients. DigiFab was also well tolerated in both study populations and no unexpected safety concerns were identified. No clinically significant abnormal laboratory values have been attributed to DigiFab, and HASA was negative in all subjects tested. Additionally post-marketing evidence provides support to the relative safety of DigiFab. The benefit-risk balance for DigiFab as a treatment for life threatening digoxin toxicity is favourable and considering the anticipated withdrawal of Digibind from the marketplace will safeguard supply of a potentially life-saving product.

9. First round recommendation regarding authorisation

It is recommended that DigiFab be approved for proposed indication of ‘Digoxin-specific antibody fragment F (Ab) (Ovine) DigiFab is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias not responsive to atropine and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.’ The approval is subject to incorporation of changes to the proposed PI.

10. Clinical questions

10.1. Pharmacokinetics

None.

10.2. Pharmacodynamics

With regard to secondary pharmacodynamic effects, it is noted that after Fab dosing in Study TAb007-02, the PTQ index decreased in both groups. However, the fall was greater in the Digibind group and the difference from the result seen in the DigiFab group was statistically significant at 8 h. This difference would suggest a continued effect of digoxin in the DigiFab (DigiTAb) group which is contrary to what one would expect from the actual results for free and total digoxin. The sponsor is to provide critical comment on this difference and whether it may or may not be of clinical significance.

10.3. Efficacy

None.

10.4. Safety

It is noted that a patient registry is currently underway in the UK to collect additional information on safety and immunogenicity associated with the use of DigiFab. Has the sponsor any intention to set up a similar registry in Australia should the drug be approved and if not, why not? Does the sponsor see any impediment in its being able to gain access to any reports which may be issued from the UK registry? Will reports from the UK registry be actively sought by the sponsor as part of its overall programme of pharmacovigilance monitoring?

11. Second round evaluation of clinical data submitted in response to questions

11.1. Pharmacodynamics

With regard to secondary pharmacodynamic effects, it is noted that after Fab dosing in Study TAb007-02, the PTQ index decreased in both groups. However, the fall was greater in the Digibind group and the difference from the result- seen in the DigiFab group was statistically significant at 8 h. This difference would suggest a continued effect of digoxin in the DigiFab (DigiTAb) group which is contrary to what one would expect from the actual results for free and total digoxin. Please provide critical comment on this difference and whether it may or may not be of clinical significance.

11.1.1. Sponsor's response

In Study TAb007-02 the DigiFab and Digibind dosing groups produced similar reductions in PTQ index values. They fell in tandem for up to 4 h post digoxin until they temporarily separated. The observed PTQ index difference between the groups is also exaggerated by the focus of attention on the graph in the study report on the time period from 0 to 12 h. The only statistically significant difference was observed at the 8 h time-point. Subsequently, the PTQ index values for the two groups converged at 48 to 168 h post-digoxin, when no further differences were observed.

The changes in the PTQ index were due to a decrease in T-wave amplitude and similar differences between the groups were observed when T-wave depression was analysed. The T-wave represents the repolarisation of the ventricles and is the most difficult of the electrocardiographic deflections to interpret with certainty. It may also change under physiological conditions such as anxiety or fear. As the serum concentrations of total digoxin decreased faster in the DigiFab group and there were no measurable concentrations of free digoxin up to 8 hr, the sponsors claim that it is difficult to explain the differences observed in T-wave depression between the two groups.

This study had a small sample size (n=8 per group; 4 male and 4 female) and the transient difference seen at 8 h may be attributable to two male subjects in the DigiFab group [information redacted] who had higher PTQ index values compared to other subjects. The two female subgroups (4 in each group) showed a comparable decrease in PTQ index values for DigiFab and Digibind. The published literature describing the relationship between PTQ index, a derived value, and digoxin concentration shows that there is considerable inter-patient variability in response and that the PTQ index responds slowly to changes in digoxin concentrations.¹⁰ The single transient difference in PTQ index seen between DigiFab and Digibind at 8 h is considered spurious and probably resulted from the small sample size and known inter-patient variability in ECG responses with digoxin, particularly in patients without digoxin toxicity (that is, healthy volunteers). Hence, the sponsors state that they would not expect the changes in PTQ index to be a reliable surrogate marker of digoxin pharmacologic activity in such a small study and they believe that the observed difference in this study of healthy volunteers is not likely to be clinically meaningful.

11.1.2. Evaluator's comments on sponsor's response

The explanation provided by the sponsors is acceptable.

11.2. Safety

It is noted that a patient registry is currently underway in the UK to collect additional information on safety and immunogenicity associated with the use of DigiFab. Does your company have any intention to set up a similar registry in Australia should the drug be approved and if not, why not? Does your company see any impediment in being able to gain access to any reports which may be issued from the UK registry? Will reports from the UK registry be actively sought by your company as part of the company's overall programme of pharmacovigilance monitoring?

11.2.1. Sponsor's response

The sponsors have highlighted the orphan drug status of the proposed product for registration, with less than 2000 cases per year requiring administration of the proposed product. Such a patient registry collects information that is voluntarily provided by physicians and patients, which only forms a small portion of the total patients exposed to the product. Based on this, the sponsor (Phebra) sees only a limited value in setting up a separate patient registry for Australia, on top of the current pharmacovigilance programme. The UK has a much larger patient population compared to Australia with similar demographics; it is believed to be a relevant and greater source of information on safety and immunogenicity associated with the use of DigiFab. Information from the UK patient registry will be readily available to Phebra as per the current safety data exchange and contractual agreements and reports from UK registry will be actively sought as part of the overall pharmacovigilance monitoring programme of Phebra. Updates and safety issues identified from the UK patient registry will be discussed in PSURs and the RMP will be updated as required.

¹⁰ Joubert, P., Kroening, B., Weintraub, M., Fleckenstein, L. Correlation between electrocardiographic changes, serum digoxin, and total body digoxin content. *Clinical Pharmacology and Therapeutics* Dec 1976 20: 676-681

11.2.2. Evaluator's comments on sponsor's response

Although the sponsors do not plan to set up a patient registry in Australia, they have confirmed that the information from the UK patient registry will be readily available to them and will be included in the updated PSURs and RMP.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of responses to clinical questions, the benefits of DigiFab in the proposed usage are unchanged from those identified in the First Round Evaluation.

12.2. Second round assessment of risks

After consideration of responses to clinical questions, the risks of DigiFab in the proposed usage are unchanged from those identified in the First Round Evaluation.

12.3. Second round assessment of benefit-risk balance

After consideration of responses to clinical questions, the benefit-risk balance of DigiFab in the proposed usage are unchanged from those identified in the First Round Evaluation.

13. Second round recommendation regarding authorisation

It is recommended that DigiFab be approved for a revised indication of:

Digoxin-specific antibody fragment F (Ab) (Ovine) DigiFab is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias not responsive to atropine and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary. However, the consequences of multiple dosing with DigiFab have not been evaluated.

The approval is subject to incorporation of changes to the proposed PI.

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