IVABRADINE & S 18982 ACTIVITIES ON HEART RATE:
A population PK/PD analysis

Vincent Duval & Christian Laveille, Clinical pharmacokinetics department, IRIS, 6 place des pléiades, F-92415 Courbevoie Cedex. E-mail: vincent.duval@fr.netgrs.com

Introduction:

The Ivabradine has been developed for its ability to decrease heart rate (HR) through it activity on the If current of the sinus node. This activity is related to both Ivabradine and S18982, its active metabolite. Pre-clinical studies demonstrated that the intrinsic activity of both entities were similar and the exposure to S18982 was roughly 40% of the Ivabradine exposure.

Aims of this analysis:

This analysis was based on phase II-III program studies. It aimed to characterize the influence of ivabradine and S18982 plasma concentrations on heart rate in the stable angina population.

Material & Method

PK and PD information issued from eight phase II- III studies were combined. Only patients from the per-protocol population were included in the analysis

- **PK data**: 3725 and 3686 plasma concentrations were available for Ivabradine and S18982
- **PD data**: different HR measurement: during **exercise tolerance tests (ETT)**: bicycle/treadmill and **at rest in supine (HRsp) & standing position (HRsd)**

Table 1: Repartition of the data over the different studies

Studies	Number of patients		Administered dose	Type of exercise	Observations			
	Placebo	Ivabradine			ETT	ECG supine	Ivabradine	S 18982
1	11	37	5, 10, 15 or 20 mg once	Bicycle	2 115	192	119	110
2	32	120	2.5, 5 or 10 mg b.i.d.	Bicycle	6 601	580	543	520
3	0	42	10, 15 and 20 mg b.i.d.	Treadmill	2 632	3357	572	570
4	0	121	5 then7.5 or 10 mg b.i.d	Treadmill	8706	0	616	604
5	181	99	5 or 7.5 mg b.i.d	Treadmill	12945	0	355	345
6	0	44	10 mg b.i.d	N/A	0	508	44	44
7	0	53	5 or 7.5 mg b.i.d.	N/A	0	397	222	217
8	338	255	7.5 or 10 mg b.i.d.	Bicycle	25 116	5704	1 254	1 276
Total	**562**	**771**			58 115	10 738	3 725	3 686

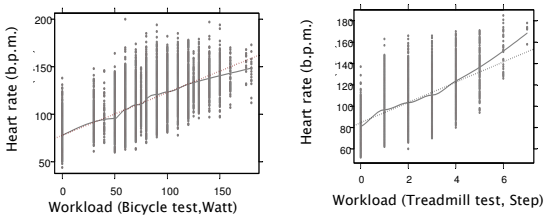
- A PK model was formerly developed on a larger patient population including the studied one: Ivabradine & S18982 were modelled independently using two two-compartment models with a first order absorption and a lag time.
- Population PK parameter estimates of the former model were fixed. Individual parameters were estimated in the current PK/PD model simultaneously with the PD parameters.

- **HR / ETT relationship without treatment**: Evaluated based on the selection & inclusion data

Covariates investigation was performed on the PD parameters based on:

- A graphical exploration of the parameters/covariates relations.
- A clinical relevance of the covariate impact.
- Improvement of the data description: comparison of the population predictions of the models, decrease in the between subject variability (BSV) and a drop in the objective function value.

Fig. 1: Relationship between heart rate and exercise test (Bicycle and treadmill test)



- **Placebo impact**:
  - Selection & inclusion visit for all patients + all the visits for the patients under placebo
  - Comparison of heart rate before and after administration of placebo.
  - Set a within subject variability (WSV) on parameters and exploration of the parameter distribution over the different periods. If no trends were observed then it would be concluded in the absence of placebo effect.
- **Treatment impact:**
  - Based on the whole dataset. A similar approach than for the placebo effect was used to evaluate the treatment impact over time
- **Responder and non responder population:**
  - Non responders= patients that didn't decrease their heart rate after treatment administration.
  - First, a mixture approach was used first with one population with Emax=0.
  - An alternative was to calculate a relative percentage of heart rate change based on individual estimated heart rate with and without treatment at the same corresponding time. The non-response was evaluated based upon the **percentage of change greater or equal to zero**.
- **Validation:**
  - Model development: 2/3 of the data,
  - Model validation on the last third,
  - Reported parameters on the whole dataset.
- **Software:** Modeling: NONMEM 5.1 (estimation: FO); Analysis: S+ 6.0

Results:

- **Without treatment or placebo:**
  - The heart rate increased **linearly** with the effort in the range of observed data: Estimation of two different slopes for the bicycle & the treadmill test. A **gender effect** on the slope during the bicycle test (HR for women increased faster during the exercise).
  - **HRsp**: differed between **genders** & decreased with **age (median age: 59 [33-86])**.
  - **HRsd** (beginning of the ETT): was related to HRsp through a **shift factor (α)** (figure 2). This factor differed between bicycle & treadmill tests.
  - **BSV** was estimated on α, HRsp & SLOP.
  - **WSV** could be estimated on HRsp & SLOP.

Fig. 2: Relationships between the different heart rates and the exercise test

$$HR_{ETT} = HR_{sd} + SLOP \cdot (WKLD\_STEP) \qquad HR_{sd} = \alpha \cdot HR_{sp}$$

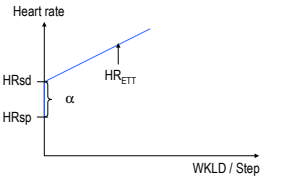
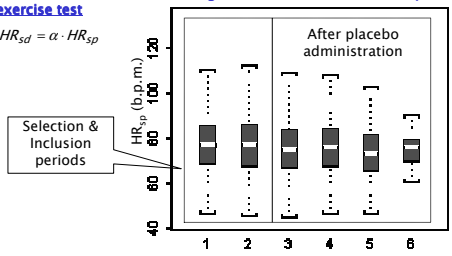


Fig. 3: Placebo influence on HRsp



- **Placebo effect:**
  - The graphical approach represented on figure 3 for HRsp, suggested the **absence of a placebo effect.** Similar results were found with the different slopes.
- **Treatment effect:**
  - An inhibition model was developed combining both drug concentrations through two different effects compartments (CeD & CeM), similar **Emax** for the two entities (preclinical data: similar intrinsic activity) & **two EC50** (EC_{50D} & EC_{50M}).
  - **BSV** on the overall treatment impact.
  - Parameters of the final model are reported on Table 2.

Impact of treatment on the different heart rates:

$$HR = (HR_{ETT} \text{ or } HRsp) \cdot (1 - Treatment)$$

$$Treatment = E_{max} \cdot \left(\frac{\frac{Ce_D}{EC_{50D}} + \frac{Ce_M}{EC_{50M}}}{1 + \frac{Ce_D}{EC_{50D}} + \frac{Ce_M}{EC_{50M}}} \right)$$

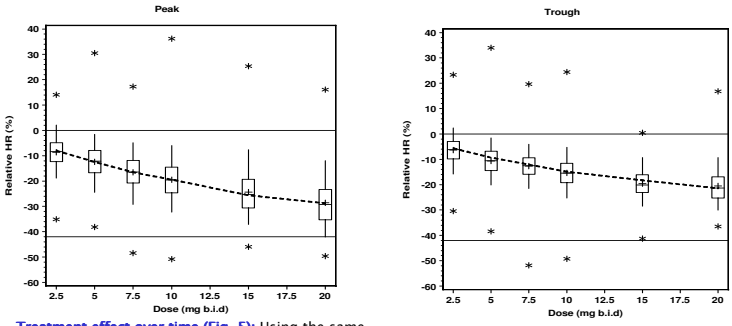
Table 2: Final parameter estimates of the model

Parameters			Param. Est. (CV)	BSV (%)	WSV (%)
HRsp (b.p.m.)	Men		71 *(0.53)*	13	8.3
	Women		76 *(1.3)*		
Age on HRsp*	%/year		0.04 *(22)*		
Shift HRsp/HRsd	Bicycle		1.04 *(0.38)*	8.8	
	Treadmill		1.14 *(0.39)*		
Slope	Bicycle (b.p.m./Watt)	Men	0.48 *(1.1)*	26	11
		Women	0.67 *(3.3)*		
	Treadmill (b.p.m./Step)		11 *(1.8)*		
Ke0D	(h^{-1})		XXX** *(15)*	146	
Ke0M	(h^{-1})		XXX** *(30)*		
Emax	(%)		XXX** *(7.6)*	26	
EC_{50D}	(ng.mL-1)		XXX** *(18)*		
EC_{50M}	(ng.mL-1)		XXX** *(24)*		
Additive res error	b.p.m.		5.4		

**: related to the difference with the median age of 59. **: Forgive us but for confidentiality reasons we cannot report these figures*

- A clear **dose/effect relationship** was established between Ivabradine administration and heart rate decrease. This relation was not obvious when each study was analyzed independently (fig.4: peak & trough are based on the HR measurements after Ivabradine administration, the dotted line: smooth in the IPRED, the boxplots are based on the observations)

Fig. 4: Dose effect relationship between Ivabradine and heart rate decrease



- **Treatment effect over time (Fig. 5):** Using the same approach as for placebo: Setting WSV on Emax, **no change** could be observed over the different treatment periods up to one year (Period 6)

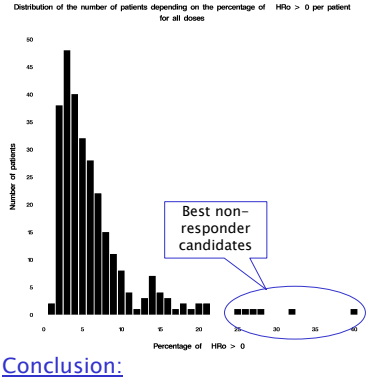
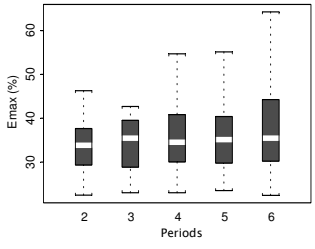


Fig 5: Treatment effect over time



- **Responder/Non responder populations:**

The mixture approach evaluate a 4% non responder population. Too small value to trust. Therefore a more pragmatic approach was used. Only 6 patients had more than 20 % of the delta heart rate above 0: Non-responder candidates. Individual Emax value for these patients are within the same range as for the other patients. It suggested an exposure problem more than a non-responder issue.

Conclusion:

Modeling exercise allowed to characterize activity related to Ivabradine and its active metabolite. Its strengthened the assumption of a dose-effect relationship between ivabradine oral administration and heart rate. No non-responder population was identified as well as no change in the treatment activity over time. Modeling has been a strong clinical pharmacology support for the phase II-III program. This model was used firstly to evaluate the impact of dosage regiment on heart rate through simulations and secondly as a base for a time-to-event analysis (Lemenuel's poster, PAGE 2005).