INVEST SECURITIES

BIOTECH

TME PHARMA

BUY

TARGET PRICE : 4,21€ +205%

ASCO JUNE 2023 + UPDATE

READ-OUT OF 15 MONTHS mOS BEFORE THE END OF JUNE !

With just a few days to go before the publication of 15-month median overall survival data, we write this note to recap the key points to bear in mind. At the end of May 2023, the company reported that five out of six patients were still alive at 14 months' follow-up. This compares with known data for the same patient profile, which shows median overall survival of 9.7 months with standard care treatments. TME Pharma's results therefore look very promising, and potentially pave the way for a new therapeutic solution in this sub-indication, provided that they are confirmed in a randomised, controlled pivotal trial involving a larger number of patients. Depending on the new data to come and discussions underway with the FDA, a Ph II PoC trial could be launched in the short term.

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14-month follow-up data: five out of six patients still alive!

At the end of May, ahead of the American Society of Clinical Oncology (ASCO) meeting from 2-6 June, TME Pharma published updated data from its Ph I/II extension study evaluating the NOX-A12/radiotherapy/bevacizumab combination in newly diagnosed patients with MGMT-unmethylated glioblastoma and incomplete resection. At 14 months follow-up, the results showed that five of the six patients in the cohort are still alive, which means that the median survival rate (mOS) has still not been reached. The mOS will be reached when half the cohort, i.e. three patients in this trial, have died, thereby providing a relative measure of the potential of the NOX-A12/radiotherapy/bevacizumab combination in terms of overall survival in this patient profile. The mOS was not reached at 14 months, which is a very good sign as it means that the patients are still responding to treatment, that the disease is probably stabilised, with tumours that are significantly reduced in size and stable, and that mOS is higher than the median overall survival known in the literature for patients of identical profile with non-methylated MGMT tumours and incomplete resection but treated with the standard of care. Indeed, the literature reports mOS of just 7.1 months for the subgroup of patients who meet the genetic profile of the TME Pharma target population and have only been treated with post-surgical RT (Kreth 2013, Annals of oncology). To date, the treatment assessed therefore shows a minimum gain of around 4.3 months, which is considerable for these patient profiles (unmethylated MGMT) who, after diagnosis and relapse, have few options available to them, and whose chances of survival at one year remain very low.

It is also worth mentioning that bevacizumab is not currently administered to patients as first-line treatment for glioblastoma, as it has not yet demonstrated any therapeutic benefit. Although there is little work distinguishing between methylated and unmethylated MGMT profiles, a paper published in 2018 (Wirsching 2018, Annals of Oncology) in elderly but newly diagnosed glioblastoma patients found no overall survival benefit with beva in addition to radiotherapy. While PFS (progression-free survival) was prolonged with the addition of beva as an add-on to RT (7.6 months vs. 4.8 months), OS was identical regardless of the methylation profile of the MGMT promoter, and irrespective of whether or not beva was added to the treatment (12.1 months vs. 12.2 months). Beva alone or in combination has never demonstrated any clinical benefit in terms of overall survival in newly diagnosed patients. On the other hand, its use is

Invest Securities and the issuer have signed an analysis services agreement.

in € / share	2023e	2024e	2025e
Adjusted EPS	-7,29	-9,09	-11,03
chg.	*n.s.*	*n.s.*	*n.s.*
estimates chg.	*n.s.*	*n.s.*	*n.s.*

au 31/12	2023e	2024e	2025e
PE	n.s.	n.s.	n.s.
EV/Sales	155,3x	313,0x	501,7x
EV/Adjusted EBITD	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.
FCF yield*	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	72,5%

* After tax op. FCF before WCR

key points	
Closing share price 15/06/2023	1,38
Number of Shares (m)	5,3
Market cap. (€m)	7
Free float (€m)	6
ISIN	NL0015000YE1
Ticker	ALTME-FR
DJ Sector	Health Technology

	1m	3m	Ytd
Absolute perf.	-28,8%	+17,4%	+13,5%
Relative perf.	-27,4%	+16,5%	+8,6%

Source : Factset, Invest Securities estimates

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recommended in relapsed patients for whom this treatment has shown therapeutic benefit. This data is interesting to compare with that from TME Pharma, as achieving a minimum mOS of 14 months with beva as an add-on to NOX-A12/RT versus 12.1 months for beva/RT already shows a potential clinical benefit in terms of overall survival. Although the TME Pharma cohort is too small to apply reliable statistics or comparisons, it appears that an improvement of at least two months in mOS can be obtained by adding NOX-A12 to RT/beva treatment, i.e. an improvement of around 16.5% at this stage.

Finally, from an anatomical point of view, 100% of patients showed a partial radiographic response in the ongoing TME Pharma study (i.e. a reduction in tumour size of more than 50%), with consistent biological results showing an increase in anti-tumour immune cells at the tumour site at the same time as a reduction in the number of pro-cancer immune cells and the rate of vascularisation.

Improvement in median overall survival so far of 44% vs. SoC

These 14-month figures are extremely encouraging, as they suggests an improvement of at least 44% in median overall survival versus standard treatment at this stage of follow-up, representing a gain of at least four additional months in median survival for these target patients. This arm of the GLORIA Phase I/II trial has shown exceptional clinical results in GBM patients with survival data to date confirming that 83% of patients are still alive at 14 months of treatment compared to standard therapies which offer an average PFS of six months and OS of 9.7 months in the precise indication targeted. In addition, note that 100% of targeted lesions treated with the NOX-A12 combination shrank by more than 50%, and that 83% of patients achieved partial responses lasting more than six months, with two of the six patients in the cohort seeing the size of their tumour shrink by more than 99% (complete regression, which is difficult to qualify as such in GBM, given that the disease is so aggressive with a poor prognosis and considered to be an incurable cancer - two-year survival rate of 18% and 4% at five years). As such, the results of the combo currently being evaluated by TME Pharma are very promising, given the impact observed at this stage on mOS, although PFS data also remains a key parameter to be assessed. To date, the company has not provided data on PFS (for the NOX-A12RT/beva tri-combination), bearing in mind that a matched historical cohort treated with standard therapy showed:

- average PFS of six months (vs 5.7 months in the GLORIA NOX-A12/RT cohort),
- mOS of 9.7 months (compared with over 14 months at this stage for the NOX-A12/RT/beva tri-combination, also to be compared with the 12.7 months obtained with the NOX-A12/RT bi-combination),
- a reduction in tumour size for only 25% of patients with the standard of care (vs. 100% for TME Pharma), while 10% of patients showed a reduction of 50% or more in tumour size when treated with the standard treatment (vs. 100% for TME Pharma).

Predictive biomarker: more information unveiled at ASCO

Alongside the extremely promising clinical data obtained to date, biological research has identified a potential biomarker that could predict the clinical response of brain cancer patients to NOX-A12 treatment. The presence of this specific biomarker is a considerable asset in the patient treatment journey, as it should enable prescribers to screen patients more effectively and select only those with a responder profile who will therefore benefit most from the therapy. In theory, this should prevent patients who are unlikely to respond favourably to treatment from losing their chances of success and, ultimately, survival. Furthermore, the presence of this predictive biomarker provides another advantage for TME Pharma, as its existence should encourage a positive assessment by evaluators and payers, who should welcome the possibility of having an effective therapy available that also benefits from a sensitive companion test. This should increase the chances of regulatory approval and commercial success for NOX-A12 (better targeting of the market and therefore a reduction in the medico-economic

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costs associated with management of GBM patients), while reducing the cost and duration of the associated clinical trials thanks to better stratification and selection of target patients.

A poster presenting data about this biomarker was presented at ASCO on 3 June 2023. The abstract highlights biomarker analyses of 10 glioblastoma patients treated with NOX-A12/RT. Patients with higher biomarker scores at baseline had a significantly longer PFS than those with lower scores (6.0 months vs. 3.0 months; p=0.031) and a trend towards prolonged OS (15.8 months vs. 11.1 months; p=0.075). However, these correlations were not observed in the reference cohort of patients treated with the standard of care (PFS: 4.6 months vs 6.0 months; p = 0.502; OS: 9.6 months vs 10.0 months; p = 0.243).

The biomarker identified by TME Pharma is calculated by analysing the frequency of expression of the NOX-A12 target, CXCL12, on two types of cells in the tumour microenvironment (TME): (i) endothelial cells (blood vessels) and (ii) glioma cancer cells. The combination of CXCL12 expression on these two key cell types in the TME gives the EG12 score, corresponding to the fraction of endothelial cells and glioma cells expressing CXCL12. This EG12 score was significantly correlated with PFS (r = 0.87; p = 0.005) in patients treated with the NOX-A12/RT combo, whereas this correlation was not observed in a reference cohort of 15 glioblastoma patients treated with standard therapy (r= -0.10; p = 0.724).

Next key milestone: median overall survival at 15 months, expected end-June

At this stage, the RT/NOX-A12/beva treatment combination has surpassed the results obtained by TME Pharma with the simple RT/NOX-A12 combination but without beva, for which mOS of 12.7 months was observed in the initial Ph I/II study, which was carried out on nine patients (with a response rate of almost 90%). This mOS of 12.7 months already represents three additional months of survival compared with standard treatment, i.e. an improvement of 31%, and the data obtained at this stage with the tri-combination shows a clearly superior clinical potential:

- reduction in the size of the target tumour (maximum reductions observed without beva ranging from -2% to -71% depending on the dose of NOX-A12 [200, 400 and 600 mg/week] versus a mean reduction of -74.9% [from -53.8% to -99.9%] with beva),
- radiographic partial response rate defined as a reduction in tumour size of more than 50% (40% without beva vs 100% with beva),
- improved overall survival (12.7 months without beva and at least 14 months with beva), although PFS data have not yet been released for the tri-combination (vs. 5.7 months for the NOX-A12/RT combo).

After this updated 14-month follow-up data, presented at the ASCO congress in early June 2023, the next event on the agenda is the publication of mOS data at 15 months follow-up, expected before the end of June. PFS data is also a key parameter that would be useful to assess in order to evaluate the benefit of tri-combination on overall survival, as well as on progression-free survival, which offers a real benefit in terms of quality of life.

Short-term newsflow

- End-June 2023: 15-month survival in the RT/NOX-A12/beva arm in GBM – Ph I/II GLORIA.
- 2023: discussions with the FDA and the EMA to validate the design of a randomised and controlled Ph II trial vs SoC – combo RT/NOX-A12 with our without beva. Launch planned for end-2023 depending on financing availabilities.

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Glioblastomas can appear at any age and their development is often very fast over two/three months. In adults, GBM is the most frequent type of brain cancer with an incidence rate of around 1/33,330 per year, and prevalence estimated at 1/100,000. According to the literature, the prevalence of unmethylated MGMT in GBM is around 30 to 40% in the US and Europe. Prevalence varies considerably depending on the population studied and the methods used to detect MGMT methylation, but it is accepted that younger patients are more likely to have a non-methylated form. Treatment is firstly surgical with the widest possible resection bearing in mind that it is generally impossible to remove the entire tumours which infiltrates the normal brain parenchyma. After surgery when possible, the first line treatment consists of targeted radiotherapy in association with chemotherapy. The benefit of these two treatments in terms of survival is nevertheless very modest, albeit proven however. In the event of a relapse, second-line chemotherapy, or even a second round of surgery may be proposed. As a result, a new solution with improved therapeutic benefits is eagerly awaited if brain cancers are to be treated more effectively.

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FINANCIAL DATA

Share information	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
Published EPS (€)	-2,54	-2,70	-0,08	-0,32	-0,26	-21,88	-7,29	-9,09	-11,03
Adjusted EPS (€)	**-2,54**	**-2,70**	**-0,08**	**-0,32**	**-0,26**	**-21,88**	**-7,29**	**-9,09**	**-11,03**
Diff. I.S. vs Consensus	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Dividend	0,00	0,00	0,00	0,00	0,00	0,00	0,00	1,00	2,00

Valuation ratios	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Sales	144,40x	20,65x	27,02x	-16,16x	4,11x	39,84x	155,29x	312,97x	501,73x
EV/Adjusted EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF bef. WCR yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	72,5%

NB : valuation based on annual average price for past exercise

Entreprise Value (€m)	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
Share price in €	*15,6*	*1,38*	*1,38*	*1,38*	*1,38*	*1,38*	*1,38*	*1,38*	*1,38*
Market cap.	36	7	7	7	7	7	7	7	7
Net Debt	*1,9*	*0,5*	*0,2*	*-9,7*	*-6,7*	*-1,5*	*15,5*	*36,7*	*62,4*
Minorities	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*1,0*	*2,0*
Provisions/ near-debt	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*
+/- Adjustments	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*1,0*	*2,0*
Entreprise Value (EV)	**38**	**8**	**8**	**-2**	**1**	**6**	**23**	**46**	**74**

Income statement (€m)	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
Sales	0	0	0	0	0	0	0	0	0
chg.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Adjusted EBITDA	-5	-4	-4	-6	-14	-28	-12	-16	-21
adjusted EBITA	**-5**	**-4**	**-4**	**-6**	**-14**	**-28**	**-12**	**-16**	**-21**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	-5	-4	-4	-6	-14	-28	-12	-16	-21
Financial result	-1	-6	3	-5	-5	-5	-5	-5	-5
Corp. tax	0	0	0	0	0	0	0	0	0
Minorities+affiliates	0	0	0	0	0	0	0	1	2
Net attributable profit	-5	-11	-1	-10	-19	-33	-17	-20	-24
Adjusted net att. profit	**-5**	**-11**	**-1**	**-10**	**-19**	**-33**	**-17**	**-20**	**-24**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***

Cash flow statement (€m)	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
EBITDA	-5	-4	-4	-6	-14	-28	-12	-16	-21
Theoretical Tax / EBITA	0	0	0	0	0	0	0	0	0
Capex	0	0	0	0	0	0	0	0	0
Operating FCF bef. WCR	**-5**	**-4**	**-4**	**-6**	**-14**	**-28**	**-12**	**-16**	**-21**
Change in WCR	0	0	0	0	0	0	0	0	0
Operating FCF	**-5**	**-4**	**-3**	**-6**	**-14**	**-28**	**-12**	**-16**	**-21**
Acquisitions/disposals	0	0	0	0	0	0	0	0	0
Capital increase/decrease	3	8	1	14	16	28	0	0	0
Dividends paid	0	0	0	0	0	0	0	0	0
Other adjustments	-1	-6	3	-5	-5	-5	-5	-5	-5
Published Cash-Flow	**-3**	**-3**	**1**	**3**	**-3**	**-5**	**-17**	**-21**	**-26**

Balance Sheet (€m)	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
Assets	0	0	0	0	0	0	0	0	0
Intangible assets/GW	0	0	0	0	0	0	0	0	0
WCR	-2	-2	-2	-2	-2	-2	-2	-2	-2
Group equity capital	-4	-3	-2	8	-6	-11	-28	-50	-75
Minority shareholders	0	0	0	0	0	0	0	1	2
Provisions	0	0	0	0	0	0	0	0	0
Net financial debt	**2**	**0**	**0**	**-10**	**-7**	**-1**	**15**	**37**	**62**

Financial ratios	2017	2018	2019	2020	2021	2022	2023e	2024e	2025e
EBITDA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EBITA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Adjusted Net Profit/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROCE	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gearing	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ND/EBITDA (in x)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Source : company, Invest Securities Estimates

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INVESTMENT CASE

TME PHARMA (ex-NOXXON) is a biotech company with an oncology-focused portfolio. The two products it has developed to date—NOX-A12 (glioblastoma, as well as metastatic pancreatic and colorectal cancer) and NOX-E36 (solid cancers)—are designed to break the tumor protection barrier and block tumor repair by neutralizing chemokines in the tumor microenvironment (TME). Its clinical approach is unique and can be used in combination with other therapeutic approaches, notably radiotherapy and immunotherapy, to weaken tumor defenses against the immune system and enable greater therapeutic impact.

SWOT ANALYSIS

STRENGTHS

- An innovative approach within the IO space
- Partnership with Merck for brain cancer
- Drugs that target indications with little competition

WEAKNESSES

- Relatively early-stage pipeline
- Need for additional financing within a year

OPPORTUNITIES

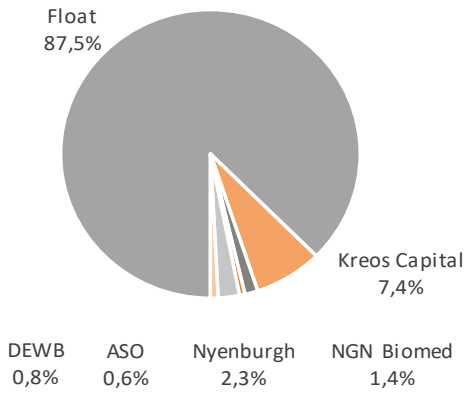
- Combination drug trials
- Possibility of new partnerships
- Significant M&A activity in the field

THREATS

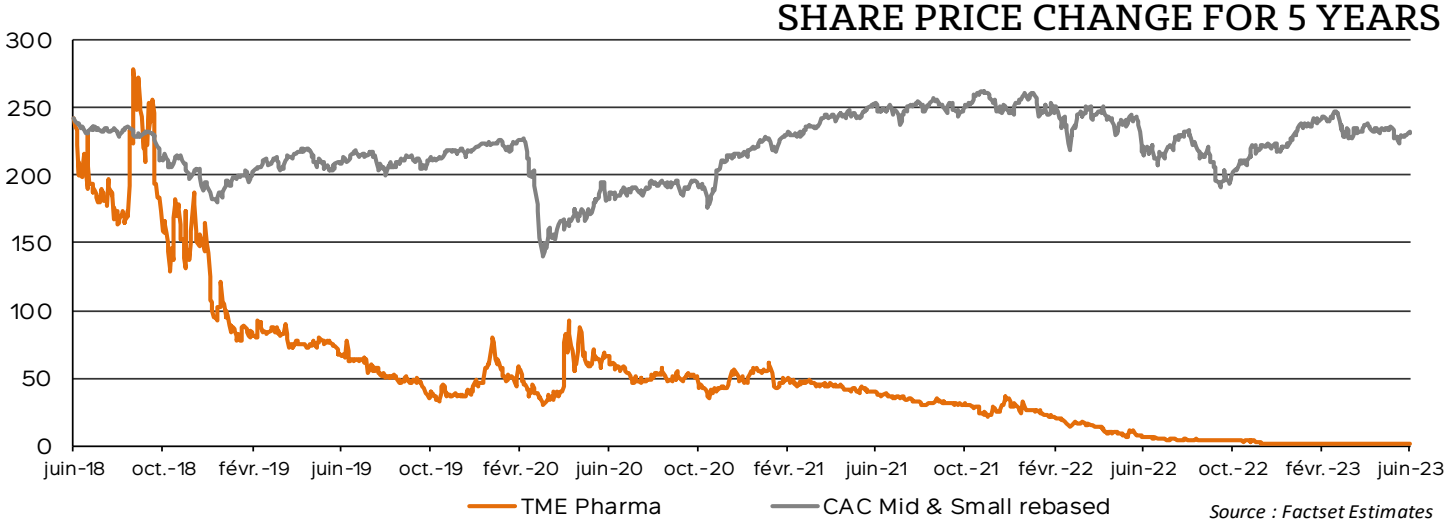
- Regulatory and clinical risks
- Legal risks
- Commercial risks

ADDITIONAL INFORMATION

Shareholders



SHARE PRICE CHANGE FOR 5 YEARS



Source : Factset Estimates

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TARGET PRICE AND RECOMMENDATION

Our analyst ratings are dependent on the expected absolute performance of the stock on a 6- to 12-month horizon. They are based on the company’s risk profile and the target price set by the analyst, which takes into account exogenous factors related to the market environment that may vary considerably. The Invest Securities analysis office sets target prices based on a multi-criteria fundamental analysis, including, but not limited to, discounted cash flows, comparisons based on peer companies or transaction multiples, sum-of-the-parts value, restated net asset value, discounted dividends.

Ratings assigned by the Invest Securities analysis office are defined as follows:

- BUY: Upside potential of more than 10% (the minimum upside required may be revised upward depending on the company’s risk profile)
- NEUTRAL: Between -10% downside and +10% upside potential (the maximum required may be revised upward depending on the company’s risk profile)
- SELL: Downside potential of more than 10%
- TENDER or DO NOT TENDER: Recommendations used when a public offer has been made for the issuer (takeover bid, public exchange offer, squeeze-out, etc.)
- SUBSCRIBE or DO NOT SUBSCRIBE: Recommendations used when a company is raising capital
- UNDER REVIEW: Temporary recommendation used when an exceptional event that has a substantial impact on the company’s results or our target price makes it impossible to assign a BUY, NEUTRAL or SELL rating to a stock

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12-MONTH HISTORY OF OPINION

The table below reflects the history of price recommendation and target changes made by the financial analysis office of Invest Securities over the past 12 months.

Company Name	Main Author	Release Date	Rating	Target Price	Potential
TME PHARMA	Jamila El Bougrini	27-mars.-23	ACHAT	4,2	+310%
TME PHARMA	Jamila El Bougrini	11-nov.-22	ACHAT	16,1	+381%
TME PHARMA	Jamila El Bougrini	15-juil.-22	ACHAT	0,2	+220%

DETECTION OF CONFLICTS OF INTEREST

	TME PHARMA
Invest Securities was lead manager or co-lead manager in a public offer concerning the financial instruments of this issuer during the last twelve months.	No
Invest Securities has signed a liquidity contract with the issuer.	Yes
Invest Securities and the issuer have signed a research service agreement.	Yes
Invest Securities and the issuer have signed a Listing Sponsor agreement.	No
Invest Securities has been remunerated by this issuer in exchange for the provision of other investment services during the last twelve months (RTO, Execution on behalf of third parties, advice, placement, underwriting).	No
This document was sent to the issuer prior to its publication. This rereading did not lead the analyst to modify the valuation.	No
This document was sent to the issuer for review prior to its publication. This rereading led the analyst to modify the valuation.	No
The financial analyst has an interest in the capital of the issuer.	No
The financial analyst acquired equity securities of the issuer prior to the public offering transaction.	No
The financial analyst receives remuneration directly linked to the transaction or to an investment service provided by Invest Securities.	No
An executive officer of Invest Securities is in a conflict of interest with the issuer and was given access to this document prior to its completion.	No
Invest Securities or the All Invest group owns or controls 5% or more of the share capital issued by the issuer.	No
Invest Securities or the All Invest group holds, on a temporary basis, a net long position of more than 0.5% of the issuer's capital.	No
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